A COMPARISON OF CLINICAL PROFILE AND OUTCOME AMONG CRITICALLY ILL PATIENTS WITH HOSPITAL ACQUIRED INFECTIONS CAUSED BY *ACINETOBACTER SPP* VERSUS OTHER BACTERIAL PATHOGENS

A Dissertation submitted in partial fulfilment of

M.D (General Medicine) branch I Examination of the Tamil Nadu

DR. M.G.R. UNIVERSITY, CHENNAI

to be held in 2015.

DECLARATION

I, Dr Ajoy Oommen John hereby declare that the dissertation entitled "A COMPARISON OF CLINICAL PROFILE AND `OUTCOME AMONG CRITICALLY ILL PATIENTS WITH HOSPITAL ACQUIRED INFECTIONS (VENTILATOR ASSOCIATED PNEUMONIA AND CATHETER RELATED BLOOD STREAM INFECTIONS) CAUSED BY *ACINETOBACTER SPP* VERSUS OTHER BACTERIAL PATHOGENS" is a bonafide original work done by me, towards the M.D. Branch-I (General Medicine) Degree Examination of the Tamil Nadu Dr. M.G.R. University, Chennai to be conducted in 2015.

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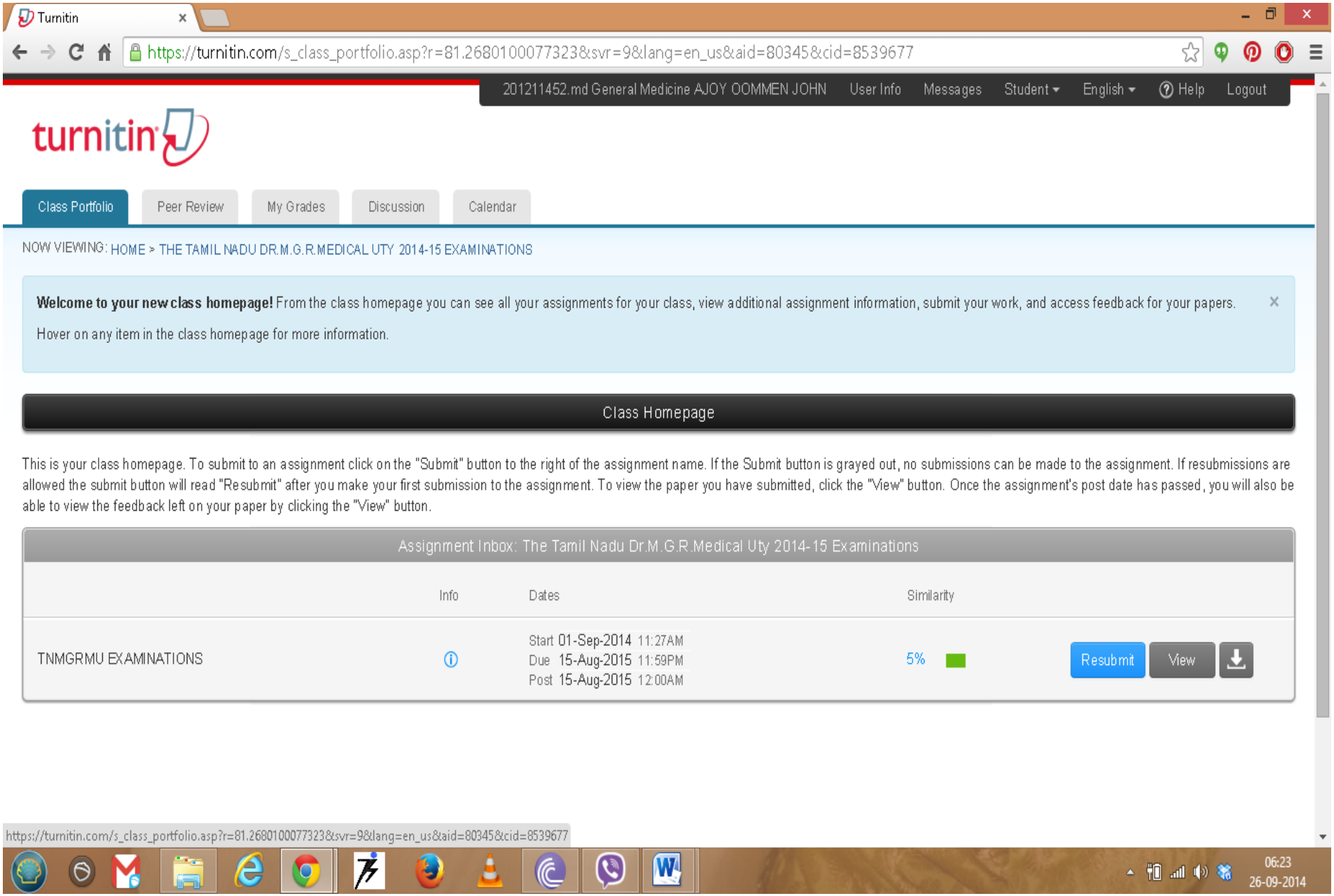
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A comparison of clinical outcomes of Hospital acquired infection (Ventilator Associated Pneumonia and Catheter related blood stream infections) among Acinetobacterspp with other bacterial pathogens among critically ill patients at a tertiary care center in South India.
Dr. Ajoy Oommen John, PG Registrar, Medicine Unit 1, Dr. O. C. Abraham, Dr. Shubhanker Mitra, Medicine, Dr. V. Balaji, Dr Shalini Anandan, Microbiology, Dr. Thomas Sudarsan, Critical Care. Medical ICU, Dr. Hema Paul, Hospital Infection Control Committee, Dr. Madhurita Singh, Surgical Intensive Care Unit.

Ref: IRB Min. No. 8159 dated 09.01.2013

Dear Dr. Ajoy Oommen John,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
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Ref: IRB Min. No. 8159 dated 09.01.2013

Dear Dr. Ajoy Oommen John,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A comparison of clinical outcomes of Hospital acquired infection (Ventilator Associated Pneumonia and Catheter related blood stream infections) among Acinetobacterspp with other bacterial pathogens among critically ill patients at a tertiary care center in South India." on January 09, 2013.

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The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Informed Consent Form (English, Tamil, Hindi and Telugu)
3. Clinical Research Form
4. Cvs of Drs. Ajoy Oommen John, O. C. Abraham, Shubhanker Mitra, Shalini Anandan, Thomas Sudarsan, V. Balaji, Madhurita Singh, Hema Paul.
5. A CD containing documents 1 - 5

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on January 9, 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
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Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS MCh	Professor, Neurological Sciences, CMC	Internal, Clinician
Dr. P. Prasanna Samuel	B.Sc, M.Sc, PhD	Professor Dept. of Biostatistics, CMC	Internal, Statistician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Dept. of Pulmonary Medicine, CMC.	Internal, Clinician
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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

A sum of Rs. 45,850/- (Rupees Forty Five Thousand Eight Hundred and Fifty only) will be granted for 17 months.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

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I would like to close by saying thanks to God, who has given me strength.

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AIM:

To compare the clinical outcomes among critically ill patients with hospital acquired infections (ventilator associated pneumonia and catheter related blood stream infections) caused by *Acinetobacter spp*. with HAI caused by other bacterial pathogens at a tertiary-care teaching hospital in South India

OBJECTIVES

Primary outcome:

a. To compare the in-hospital mortality rates of Hospital Acquired infections (HAI) caused by *Acinetobacter spp*. with that of other HAI caused by non-*Acinetobacter* bacterial HAI's among critically ill patients admitted in ICU and HDU.

Secondary outcomes:

b. Microbiological Measurements:
    i. To study the proportion of ventilator associated pneumonia(VAP) and blood stream infection (BSI) caused by *Acinetobacter* species in the Medical Intensive Care unit (MICU) and the Medical High dependency care unit (MHDU) and Surgical Intensive Care unit (SICU).
    ii. To study the antibiotic susceptibility profiles of the isolates of *Acinetobacter* species

c. Clinical Outcome: To compare the following between *Acinetobacter spp*. and Non-*Acinetobacter* hospital acquired infections
    i. Duration of mechanical ventilation (assessed by duration of ventilator free days)
    ii. Duration of ICU stay
    iii. Duration of hospital stay

ABSTRACT

TITLE: A COMPARISON OF CLINICAL PROFILE AND OUTCOME AMONG CRITICALLY ILL PATIENTS WITH HOSPITAL ACQUIRED INFECTIONS CAUSED BY *ACINETOBACTER SPP* VERSUS OTHER BACTERIAL PATHOGENS

DEPARTMENTS INVOLVED: Department of Medicine, Division of critical care, Department of Microbiology, Hospital Infection Control

KEY WORDS: *Acinetobacter*, Hospital Acquired infection, Ventilator associated pneumonia, Central line related blood stream infection, mortality, ventilator free days,

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PURPOSE: *Acinetobacter* species is being identified as a causative agent in increasingly larger proportion of hospital acquired infections (HAI). They are most commonly seen in an ICU setting, among critically ill patients. We attempted to answer the question of whether HAI caused by *Acinetobacter* species has poorer clinical outcomes when compared to HAI caused by other bacterial pathogens.

OBJECTIVES:

To compare the in-hospital mortality rates, duration of mechanical ventilation (assessed by duration of ventilator free days), duration of ICU stay and duration of hospital stay of patients with Hospital Acquired infections (HAI) caused by *Acinetobacter spp*. with HAI by other organisms.

METHODS:

This was a prospective cohort study among adult patients who developed a new fever 48 hours after admission in the Intensive Care Unit. If the patient fulfilled criteria for VAP or CR-BSI, then the patient was recruited into the study. The patients were followed up until death or discharge. The microbiological and clinical outcomes that were relevant were collected and analysed.

RESULTS:

126 patients developed a HAI, during the course of the study period, of which 93 (73.8%) were VAP and 33 (26.1%) were CR-BSI, 77 (61%) developed *Acinetobacter* related HAI and 49 (39%) were Non-*Acinetobacter* related HAI. There were 44 deaths (57.1%) among the *Acinetobacter* group compared to 33 (42.9%) in the Non-*Acinetobacter* group but this difference was not statistically significant (CI- 0.935-3.99, p=0.074). 67 out of 93 cases of VAP (72%) were caused by *Acinetobacter* spp. The *Acinetobacter* group had more patients with 0 ventilator-free days (duration of mechanical ventilation >28 days or death) when compared to the Non-*Acinetobacter* group (45 patients, 57.2% vs 12 patients, 46.2%, p= 0.03).The duration of ICU stay and hospital stay was not significantly different between the two groups.

CONCLUSIONS

In our cohort study of critically ill medical and surgical patients with VAP or CR-BSI, we found no significant increase in mortality rates among those with *Acinetobacter* related HAI's compared to those with Non-*Acinetobacter* related HAI. However we found that the patients with *Acinetobacter* related HAI's had significantly poorer ventilator outcomes (death or >28 days on Ventilator) but no significant increase in ICU or Hospital stay.

INTRODUCTION

The evolution of technology and modern medicine over the last century has led to a transformation in the practice of medicine. There has been a dramatic increase in life expectancy, and hitherto untreatable diseases have become easily treatable and even curable such that the affected person can return to a normal and productive life.

However all these apparently miraculous cures come at a price. The elimination of old foes with modern medicine has led to the emergence of new ones, as well as re-emergence of old enemies which have adapted to live in their new environment. The age of 'super-antibiotics' have been short lived due to the emergence of 'super-bugs' that have rapidly attained resistance to them.

In the last half century the number of intensive care units around the world has increased, and with it has increased the accessibility of their services. The Society for critical care medicine has quoted an increase in ICU bed numbers from 67,357 in 2007 to 944,277 beds from 2007-2009 in the United states. (1). Numbers in India are not yet clearly defined, and the data collection for the same still in progress as of 2014. (2) But one thing that is clear is that the numbers, the access and the awareness about the need for critical care in a developing country like India is increasing, although still far from adequate to meet the needs of the country.

In this setting, the emergence of ICU acquired infections plays a major role. In a country like India, the epidemiology of patients admitted in the ICU is drastically different from that in

the west. Tropical infections such as malaria, Leptospirosis etc. form a large part of our ICU disease profile.(3) These infections have a rapid progression and severity, but since the affected individuals are commonly younger, and the disease state potentially curable, there is a better associated prognosis. In this background a patient developing an ICU acquired infection, especially one that is multidrug resistant, changes their prognosis drastically.

The emergence of hospital associated and device associated infections has increased the world over.(4) These infections have been shown to adversely affect patient outcomes. Hence there is an urgent need for study of mechanisms to prevent these infections, as well as methods to treat the affected patients. There is a dearth of data in India regarding *Acinetobacter* infections, their susceptibility patterns and their associated mortality or morbidity.

This study aims to better understand the morbidity and mortality associated with Health care associated *Acinetobacter* infections. It also aims to document the antibiotic susceptibility patterns of these infections in a tertiary care center in South India.

HEALTH CARE ASSOCIATED INFECTIONS

Definition

"Healthcare-associated infections (HCAI) are infections occurring after exposure to healthcare, often, but not always, as a consequence of this exposure. Hospital acquired infections (HAI), also referred to as 'nosocomial infections' (NI) or simply 'hospital infections', are infections occurring during a stay in hospital that were neither present nor incubating at the time of hospital admission.[i]

Since the usual duration of time required to differentiate a community acquired infection which is still incubating, from a newly acquired infection after arrival at the hospital is about 48 hours, this is usually taken as the cut off time in epidemiological surveillance systems.

Epidemiology

Nosocomial infections are a major public health and patient safety issue. With increasing hospitalisation, the incidence of hospital acquired infections as well as the cost involved in patient care has become major issues especially in the west. A study conducted in 2002 estimated the number of HAI's in the United States in 1 year to be approximately 1.7 million, with 98,987 HAI associated deaths. (5) The direct costs to the healthcare system in

supporting these patients are also immense, with estimates ranging between 28.4-33.8 billion dollars a year in the United States. (6)

In 2011 the World Health Organisation undertook a Systematic review of the literature regarding health care associated infections and found that there is a scarcity of information regarding the magnitude of hospital acquired infections. Most of the data available worldwide is from the developed countries. Even the little data that is available from the developing nations usually represents only single center or a single local area incidence and prevalence. Hence the burden upon the patient, their families and the healthcare system is under-recognised.

The available literature indicates a 2-3 fold increased incidence of ICU acquired infections in low and middle income countries as compared to the high income countries. (4)(7)In addition, a patient who develops a nosocomial infection has an additional length of hospital stay that can vary from 5-29.5 days, with excess mortality ranging from 18%-30%. (4)

In India studies have estimated an incidence rate of 6-17% among patients admitted in the ICU, which included both surgical site infections as well as device associated infections. (8)(7).Device associated infections such as Catheter related blood stream infections (CRBSI), Ventilator Associated Pneumonia (VAP) and Catheter related Urinary tract infections (CRUTI) form a large majority of these infections. Of these VAP and CRBSI have been found to have the highest incidence rates ranging from 21 to 32 and 0.48 to 16 per 1000 device days respectively. (9)(8)

VENTILATOR ASSOCIATED PNEUMONIA

Definition

Precisely defining a Ventilator Associated Pneumonia (VAP) is an ongoing debate due to the lack of objective clearly identifiable criteria that can differentiate a VAP from a whole host of pulmonary disorders that can affect a critically ill patient on a ventilator. Over the years, numerous societies and institutions have put forward different criteria for the diagnosis of VAP.

Diagnosis- CPIS score

A 2005 guideline on management of hospital acquired infections was jointly put forward by the American Thoracic Society and the Infectious Disease Society of America, which broadly defined a VAP as an pneumonia occurring in mechanically ventilated patients after 48 hours of intubation, with a new or progressing infiltrate, signs of systemic inflammation, changes in sputum characteristics and a causative organism which is identified.(10) The above criteria formed the backbone for numerous other criteria and definitions for identification of VAPs. Among these the Clinical Pulmonary Infection

Score (CPIS), is one of the most widely used methods for diagnosis. It was initially put forward in 1991(11) and it uses a combination of weighted clinical and microbiological criteria for the diagnosis of VAP. (Refer Figure 1).

Figure 1

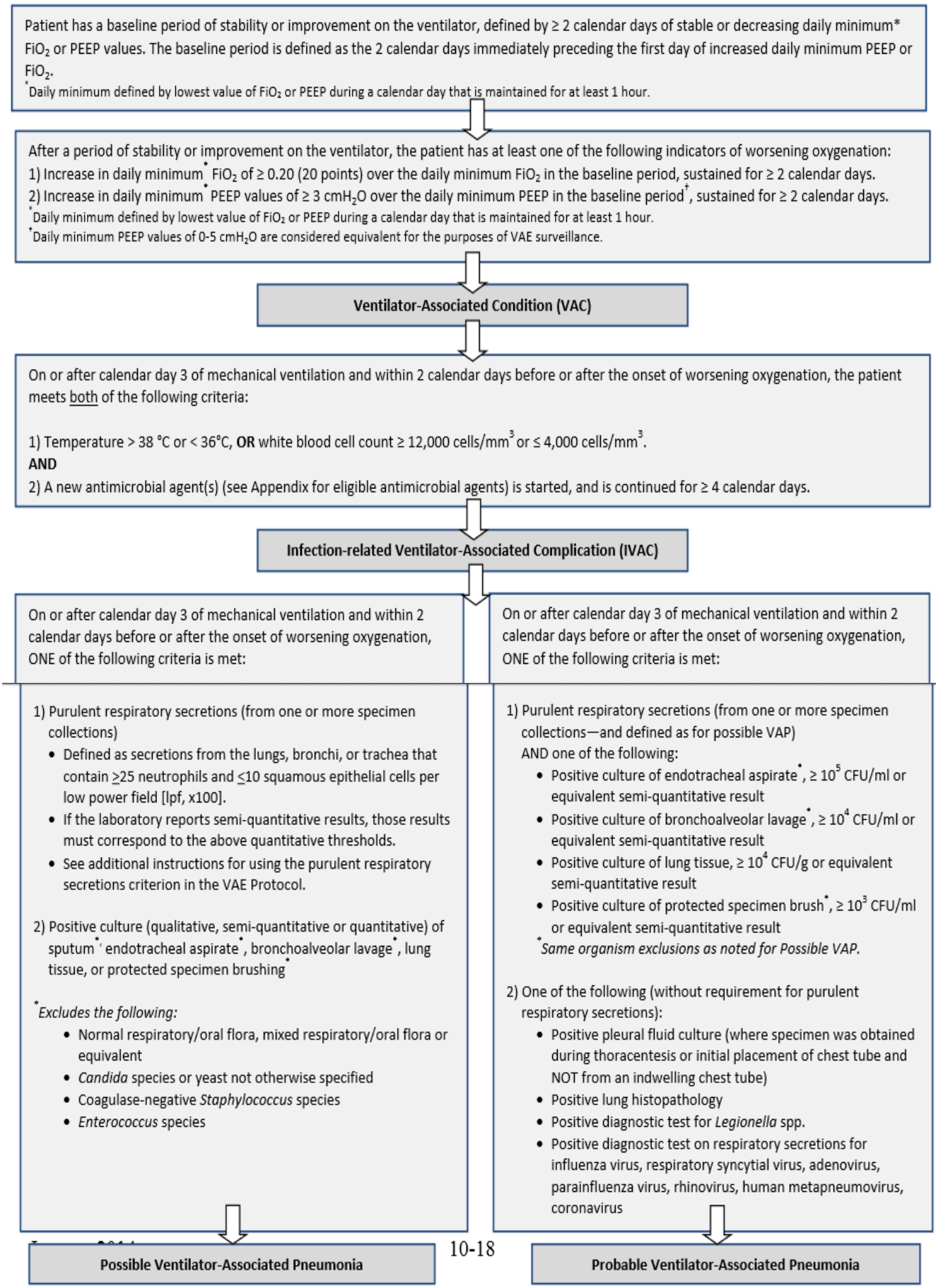
Clinical Parameter	Points
Temperature (°C)	
≥ 36.5 and ≤ 38.4	0
≥ 38.5 and ≤ 38.9	1
≥ 39.0 or ≤ 36.0	2
Blood leukocytes (x 10^3/mm^3)	
≥ 4 and ≤ 11	0
< 4 or > 11	1
Band forms ≥ 50%	Add 1
Tracheal secretions	
Absent	0
Nonpurulent	1
Purulent	2
Oxygenation: PaO_2:FiO_2 (mm Hg)	
> 240 or ARDS	0
≤ 240 and no evidence of ARDS	2
Infiltrate on pulmonary radiography	
None	0
Diffuse or patchy	1
Localized	2
Pathogenic bacteria on tracheal-aspirate culture	
Rare, light quantity, or no growth	0
Moderate or heavy quantity	1
Also seen on Gram's stain	Add 1

PaO_2 = arterial partial pressure of oxygen; FiO_2 = fraction of inspired oxygen; ARDS = acute respiratory distress syndrome.

A study done to assess the accuracy of the CPIS score showed a sensitivity of 45.8% and specificity of 60.4%, when used at a cut off value of 6, and using autopsy findings as the gold standard. (12) Earlier studies showed variability in sensitivity and specificity ranging from 72% to 77% and 85% to 42% respectively. (13,14) In addition, this score was found to be subjective, with high inter observer variability (kappa-0.16) (15). The drawbacks of poor sensitivity and subjectivity of the scoring system has prompted a re-look at how we diagnose ventilator associated pneumonias.

CDC diagnostic guidelines

In 2011 the Centers for Disease Control and Prevention (CDC) convened a working group, to propose a new approach to the diagnosis of ventilator associated pneumonias. The primary purpose of this group was to make the definition objective, streamlined and potentially automatable. This new definition, which was implemented in January 2013 by the National Healthcare Safety Network (NHSN), identifies a broad range of conditions identified as Ventilator Associated Events (VAE). Within this are three definition tiers called Ventilator Associated Condition (VAC), Infection-related Ventilator Associated Condition (IVAC) and Possible and Probable VAP.(16)


Patient has a baseline period of stability or improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily minimum* FiO_2 or PEEP values. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum PEEP or FiO_2.
*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for at least 1 hour.
After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:
1) Increase in daily minimum* FiO_2 of ≥ 0.20 (20 points) over the daily minimum FiO_2 in the baseline period, sustained for ≥ 2 calendar days.
2) Increase in daily minimum* PEEP values of ≥ 3 cmH_2O over the daily minimum PEEP in the baseline period†, sustained for ≥ 2 calendar days.
*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for at least 1 hour.
†Daily minimum PEEP values of 0-5 cmH_2O are considered equivalent for the purposes of VAE surveillance.
Ventilator-Associated Condition (VAC)
On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:
1) Temperature > 38 °C or < 36°C, OR white blood cell count ≥ 12,000 cells/mm^3 or ≤ 4,000 cells/mm^3.
AND
2) A new antimicrobial agent(s) (see Appendix for eligible antimicrobial agents) is started, and is continued for ≥ 4 calendar days.
Infection-related Ventilator-Associated Complication (IVAC)
On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:
1) Purulent respiratory secretions (from one or more specimen collections)
• Defined as secretions from the lungs, bronchi, or trachea that contain ≥25 neutrophils and ≤10 squamous epithelial cells per low power field [lpf, x100].
• If the laboratory reports semi-quantitative results, those results must correspond to the above quantitative thresholds.
• See additional instructions for using the purulent respiratory secretions criterion in the VAE Protocol.
2) Positive culture (qualitative, semi-quantitative or quantitative) of sputum*, endotracheal aspirate*, bronchoalveolar lavage*, lung tissue, or protected specimen brushing*
*Excludes the following:
• Normal respiratory/oral flora, mixed respiratory/oral flora or equivalent
• Candida species or yeast not otherwise specified
• Coagulase-negative Staphylococcus species
• Enterococcus species
Possible Ventilator-Associated Pneumonia
On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:
1) Purulent respiratory secretions (from one or more specimen collections—and defined as for possible VAP)
AND one of the following:
• Positive culture of endotracheal aspirate*, ≥ 10^5 CFU/ml or equivalent semi-quantitative result
• Positive culture of bronchoalveolar lavage*, ≥ 10^4 CFU/ml or equivalent semi-quantitative result
• Positive culture of lung tissue, ≥ 10^4 CFU/g or equivalent semi-quantitative result
• Positive culture of protected specimen brush*, ≥ 10^3 CFU/ml or equivalent semi-quantitative result
*Same organism exclusions as noted for Possible VAP.
2) One of the following (without requirement for purulent respiratory secretions):
• Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
• Positive lung histopathology
• Positive diagnostic test for Legionella spp.
• Positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus
Probable Ventilator-Associated Pneumonia

10-18

Figure 2: Ventilator-Associated Condition (VAC)

Patient has a baseline period of stability or improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily minimum* FiO_2 or PEEP values. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum PEEP or FiO_2.

*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for at least 1 hour.

AND

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

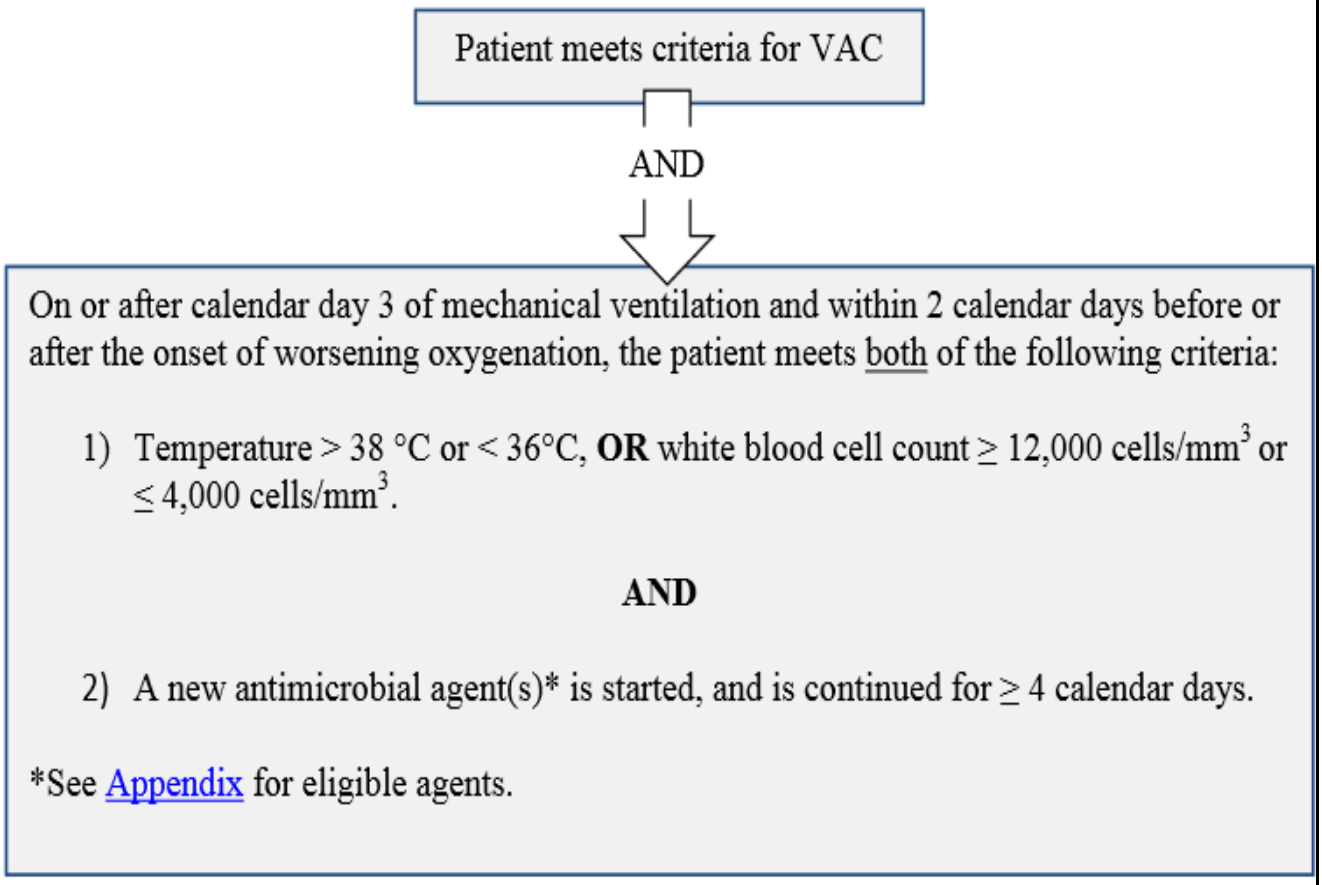
1) Increase in daily minimum* FiO_2 of ≥ 0.20 (20 points) over the daily minimum FiO_2 in the baseline period, sustained for ≥ 2 calendar days.

2) Increase in daily minimum* PEEP values of ≥ 3 cmH_2O over the daily minimum PEEP in the baseline period†, sustained for ≥ 2 calendar days.

*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for at least 1 hour.

†Daily minimum PEEP values of 0-5 cmH_2O are considered equivalent for the purposes of VAE surveillance.

Figure 3: Infection-related Ventilator-Associated Complication (IVAC)



Pathophysiology

An understanding of the potential mechanisms contributing to the development of a VAP is essential for formulating preventive strategies and improving patient care. The Endotracheal tube itself is an important factor for the development of a VAP, as it impairs the mucociliary clearance of secretions, while itself acting as an irritant thereby increasing the respiratory secretions. The cuff of the ET tube can prevent major aspirations, although the inability to provide a perfect seal, causing leakage of secretions from the sides of the cuff, facilitating micro-aspirations. These micro-aspirations are carried along by gravity to the dependent portions of the lung, where they settle, thus forming a nidus for infection.(17)

In addition the ET tube also serves as a focus of infection by being a foreign body amenable to biofilm formation by pathogenic organisms. This biofilm is a complex matrix of polysaccharides, protein and DNA which serve as a mechanical barrier between the micro-organisms and the host.(18) This in turn facilitates growth of the organisms thus increasing risks of developing an infection. The biofilm also facilitates development of antibiotic resistance, by complex interactions between organisms, as well as by decreasing the direct access of antimicrobials to the organisms.(19) Since most biofilms are produced by gram-negative organisms, it seems logical that they are the most common causative agents for VAP.

Finally, the host-microbe interaction and the balance between the two plays a vital role in determining the course of the infection and the ultimate outcome for the patient.(20)

Clinical significance

Ventilator associated pneumonias are associated with an increased mortality, with estimates of attributable mortality being approximately 10%(21,22). The cause for the increased mortality is estimated to be a consequence of the increased length of stay in the ICU, as well as the severity of the underlying illness affecting the patient. The increase in Length of hospital stay caused by a VAP has been estimated to be 2.03 days. (23) Along with the increase in hospital stay there is an associated increase in the cost to patients. In a developing country like India where costs for health care are borne by the individual patients the financial burden caused by a VAP has long term consequences for the future of the patient's entire family.

The causative organism for the VAP has been found to be an independent predictor of mortality, with high risk organisms such as Pseudomonas, *Acinetobacter* species and Xanthomonas maltophila being associated with a mortality rate of 65 %. (24)

The increased mortality, the multidrug resistant causative organisms and the increased hospital stay and associated healthcare costs make the prevention, early identification and treatment of VAP a high priority among health care providers in the Intensive Care setting.

Prevention:

Due to the greater understanding of pathophysiology of development of VAP, and its associated poorer prognosis, there has been an increased attention to preventive strategies. These strategies are aimed at, prevention of pooling of secretions, prevention of leakage from the ET tube by modifications of the tube and inhibition of biofilm formations.

- Body positioning

Current evidence based guidelines recommend that patients who are being mechanically ventilated should be placed in a semi- recumbent position, with head end elevation to 30-45 degrees. The biological reasoning for this strategy is that, in critically ill patients the gastric pH is more alkaline than in healthy adults due to the enteral feeding, as well as stress ulcer prophylaxis. This can lead to higher risk of gastric mucosal colonisation by enteric organisms. Gastroesophageal reflux of this acid can be aspirated which in turn leads to infections.

The benefit of body positioning was demonstrated in a study where mechanically ventilated patients were randomised to semi-recumbent and supine positions and the position assessment was done once a day. It was found that there was a 75% reduction in the rate of VAP in the recumbent position group compared to the supine position group (8% vs 34% respectively, p=0.03)(25). Thus, semi-recumbent body position for the prevention of VAP has become the standard of care.

- Coated ET tube

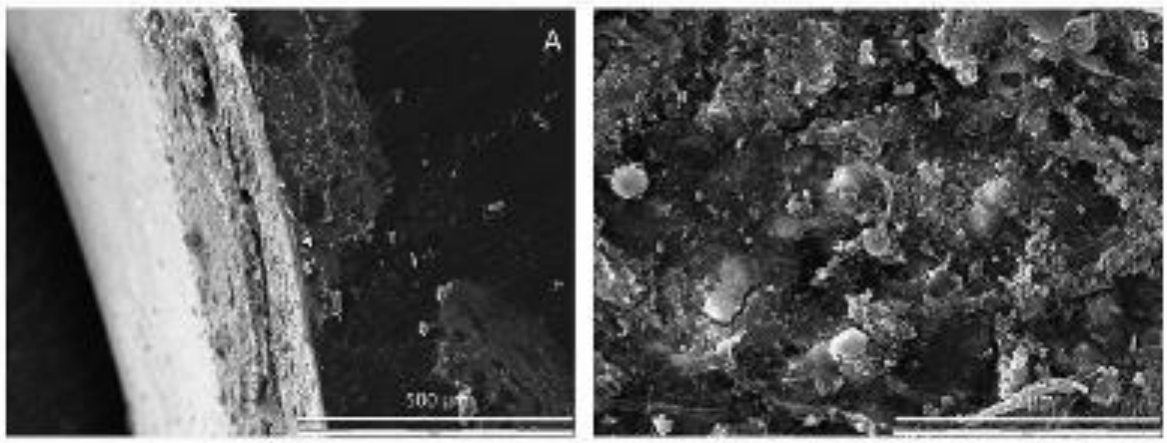


Figure 4: Scanning Electron Micrograph of an Endo-tracheal tube showing biofilm formation over the surface. B- RBC's, macrophages, epithelial cells and cocci in pairs and chains embedded within the biofilm.

The formation of biofilm is believed to play a role in shielding organisms from the effect of antibiotics, as well as providing an environment for bacterial growth and colonisation. Hence, using ET tubes coated with various antimicrobial agents have been tried. Of the agents used, chlorhexidine and sulfadiazine have been found to be of benefit in preventing biofilm formation and subsequent lung colonisation in animal models.

However, problems faced with the use of biofilm inhibitors have been mucosal reactions to the chemicals used and as a result only silver sulfadiazine has been used in clinical trials. Another problem with coated ET tubes is that the effect of the coating is short lived. This is due to the ability of the gram negative organisms to form a biofilm over the coating. The Mucus Shaver is a device designed with a silicone rubber balloon with 2 or more rings which can effectively remove the secretions and bacterial biofilm and thus enable the ET tube

coating to maintain its efficiency. This device was tested in a randomised control trial involving 24 patients where the control arm received tracheal suctioning only while the treatment arm received tracheal suctioning with Mucus Shaver clearance of the ET tube sixth hourly until extubation. It was found that only 1 of 12 patients in the study group had colonisation as compared to 10 of 12 in the control group ($p<0.01$). There was no significant adverse effect associated with the use of the Mucus Shaver. (20)

The use of biofilm-inhibitor coated ET tubes have not gained wide acceptance due to the limited number of human studies that have been done, and the questionable benefit observed in these studies. The cost involved in the use of this equipment has been another deterrent to its widespread usage. A list of the different biofilm-inhibitors that have been tried is given below:

Category	Mechanism of Action	Studied Coating Types
Antimicrobial	Silver and sulfadiazine have cytotoxic and cytostatic properties by binding to DNA and other compounds. Chlorhexidine causes structural changes in cellular membrane, facilitating silver and sulfadiazine entry into the cell.	Silver sulfadiazine Silver sulfadiazine and chlorhexidine Silver sulfadiazine and carbon Silver sulfadiazine, chlorhexidine and carbon
Oligodynamic iontophoresis	Coating polymer and biological fluids contact causes release of silver ions. The reaction is counterbalanced by the movement of electrons from silver to platinum or another element, creating a low voltage local electric current.	Silver and carbon Silver/platinum Silver/platinum
Photodynamic	Photosensitizer pigments release singlet oxygen when exposed to ultraviolet light.	Rose bengal

Table 1: Endotracheal tube coating used to inhibit biofilm formation

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- Subglottic Drainage of secretions

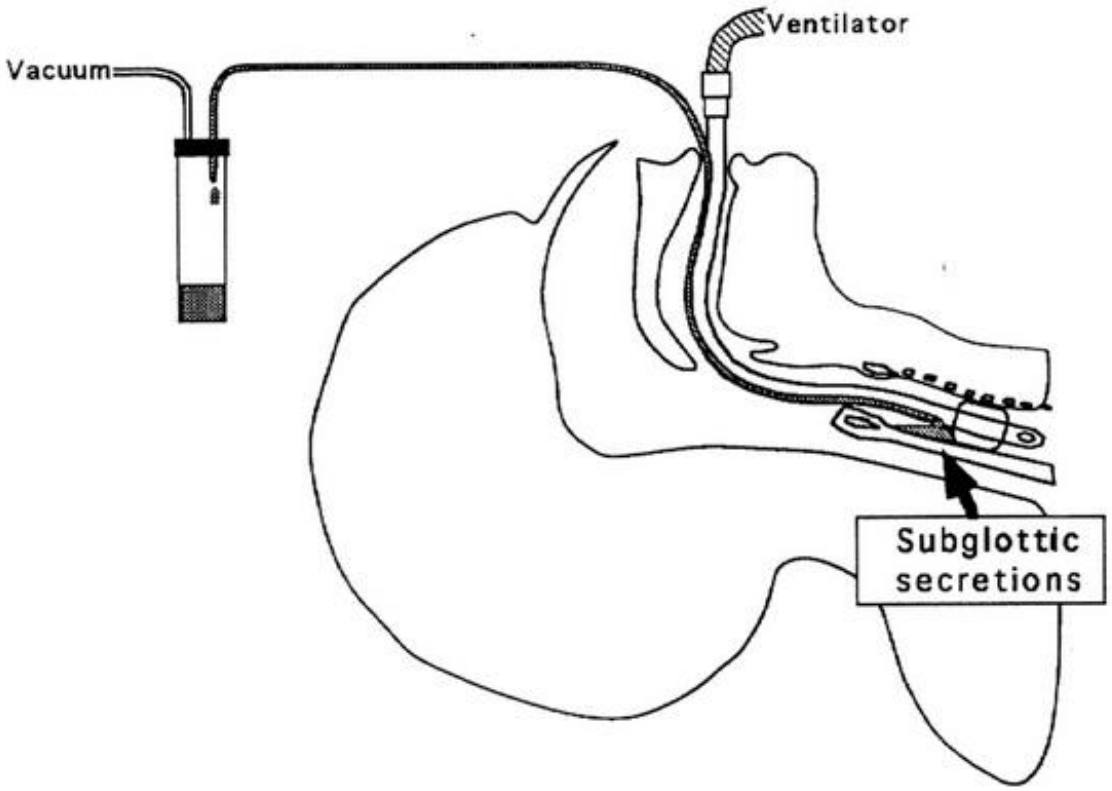


Figure 5: Schematic representation of a continuous subglottic secretion drainage system

The irritative effect of an ET tube and the obstruction caused by it hampers the normal functioning of the ciliary processes of the respiratory epithelium. This in turn leads to impaired clearance of respiratory secretions. These secretions can leak past the ET tube, due

to the imperfect seal produced by it and then track down into the lung causing infection. In order to break this cycle attempts have been made to improve the seal produced by the cuff of the ET tube, or to suction the secretions before they reach the lung parenchyma thereby preventing infection.

Normal suctioning of the tube is inadequate as it is unable to clear the secretions and mucus that accumulates at the very tip of the ET tube. Hence ET tubes have been designed with specialised tips that allow for suctioning of the subglottic portion of the tube. This suctioning can either be intermittent or continuous. The debate about which of these is superior is an ongoing one.

The use of suction for subglottic drainage of secretions was studied in a systematic review, and found that its use was associated with decreased duration of ICU stay, decreased duration of mechanical ventilation and an increase in time to first VAP. There were no associated adverse effects from the use of this device. (26)

CATHETER RELATED BLOOD STREAM INFECTIONS

Epidemiology

Central venous catheters (CVC) are being used with increasing frequency in hospitals both in an ICU setting as well as outside ICU's. The infection of these CVC's is becoming an increasingly large problem worldwide. The incidence of central line infections in the USA is estimated to be 1.65 per 1000 central line days amounting to 23,000 infection events.(27). This number is higher in the developing countries, with a large surveillance study conducted among ICU's in Latin America, Asia, Africa and Europe reporting a pooled rate of 6.8 per 1000 central line days. (28). Studies done in India have also reported infection rates ranging from 8.75-9.6 per 1000 central line days. (29,30).

One possible reason for the increased incidence in the developing countries is the lack of strict adherence to aseptic precautions during insertion of the lines, as well as the lack of clearly defined central line care bundles.

Clinical features

The importance of CRBSI is evident from the increased mortality that it causes, with one recent systematic review estimating almost two fold increased risk of mortality among those with CRBSI, even after matching for severity of illness. (31) Another study

estimated an increase in ICU stay by 13 days in those with CRBSI and a crude mortality rate of 28% (32).

Risk factors

The risk factors for CRBSI can be classified a patient, personnel and device related factors.

The patient related factors include the degree of severity of the underlying illness, immunosuppression especially granulocytopenia, malnutrition, loss of integrity of skin especially in burns. (33)

Operator related factors include degree of adherence to aseptic technique during placement of the line, as well as catheter site care.

Catheter related factors are the site of placement of the line, the duration of the line and characteristics of the line such as the material, number of lumens etc. (34)

Definitions

The NHSN monitors the CRBSI, and publishes data on the yearly incidence of CRBSI.

The surveillance definition used by the NHSN is:

“Isolation of a recognized pathogen from blood culture(s), the presence of clinical signs of sepsis and/or shock (e.g., fever, chills, or hypotension), a determination that the infection is not from other sources, and confirmation that the organism is not a contaminant”(35).

Diagnostic criteria and methods

Although the above definition serves as a useful guide, the clinical diagnosis of a catheter related infection still remains difficult because the clinical signs of inflammation at the catheter site are specific but not sensitive, and hence may not always be present. Secondly the clinical signs of systemic inflammation are very nonspecific and can be caused due to a host of other reasons, especially in a critically ill patient.

For a patient with a suspected CRBSI, paired blood samples drawn from both the central line and a peripheral vein must be labelled and sent to the laboratory. One study demonstrated that if samples were not drawn from all the lumens of a multi-lumen catheter, then the infection could be missed in almost 30% of the patients. (36) If a sample cannot be obtained from the central line, then two or more samples need to be taken from the catheter lumen and sent for culture. However, the need for cultures from all the lumens is not well defined in this setting.(37).

Numerous methods for the diagnosis of CRBSI are available, with some necessitating catheter removal for facilitation of diagnosis, and other newer methods where the catheter can remain in place. These methods are listed in Table 1

	Diagnostic Method	Description	Criteria for Positivity	Sensitivity, %	Specificity, %
Methods not requiring CVC removal	Qualitative blood culture through device	One or more blood cultures drawn through CVC	Any growth	87	83
	Quantitative blood culture through device	Blood culture drawn through CVC, processed by pour-plate methods or a lysis-centrifugation technique	≥100 CFU/mL	77	90
	Paired quantitative blood cultures	Simultaneous cultures drawn through CVC and percutaneously	Both cultures positive with CVC culture yielding 5-fold higher or more than peripherally drawn culture	87	98
	Differential time to positivity	Simultaneous blood cultures drawn, through CVC and percutaneously, and monitored continuously	Both cultures positive with CVC positive ≥2 h earlier than peripherally drawn culture	85	81
Methods requiring CVC removal	Qualitative catheter segment culture	Segment from removed CVC is immersed in broth media and incubated for 24-72 h	Any growth	90	72
	Semiquantitative catheter segment culture	A 5-cm segment from removed CVC is rolled 4 times across a blood agar plate and incubated	≥15 CFU	85	82
	Quantitative catheter segment culture	Segment from removed CVC is flushed or sonicated with broth, serially diluted, plated on blood agar, and incubated	≥1,000 CFU	83	87

CFU, colony-forming units; **CRBSI**, catheter-related bloodstream infection; **CVC,** central venous catheter

Adapted from reference 22.

Table 1: Methods for the diagnosis of a central line infection(38)

Paired quantitative blood cultures are considered to be the gold standard for diagnosis, but are time consuming and more expensive. On the other hand newer semi qualitative and radiometric methods have been developed that facilitate more rapid identification of growth in culture, and are less expensive. In addition the use of differential time to positivity (the detection of positivity in a blood culture drawn from a central line 2 more hours before the detection of positivity from a simultaneously drawn peripheral blood culture) has been demonstrated to be an accurate predictor of CRBSI. (39)

ACENITOBACTER BAUMANNII

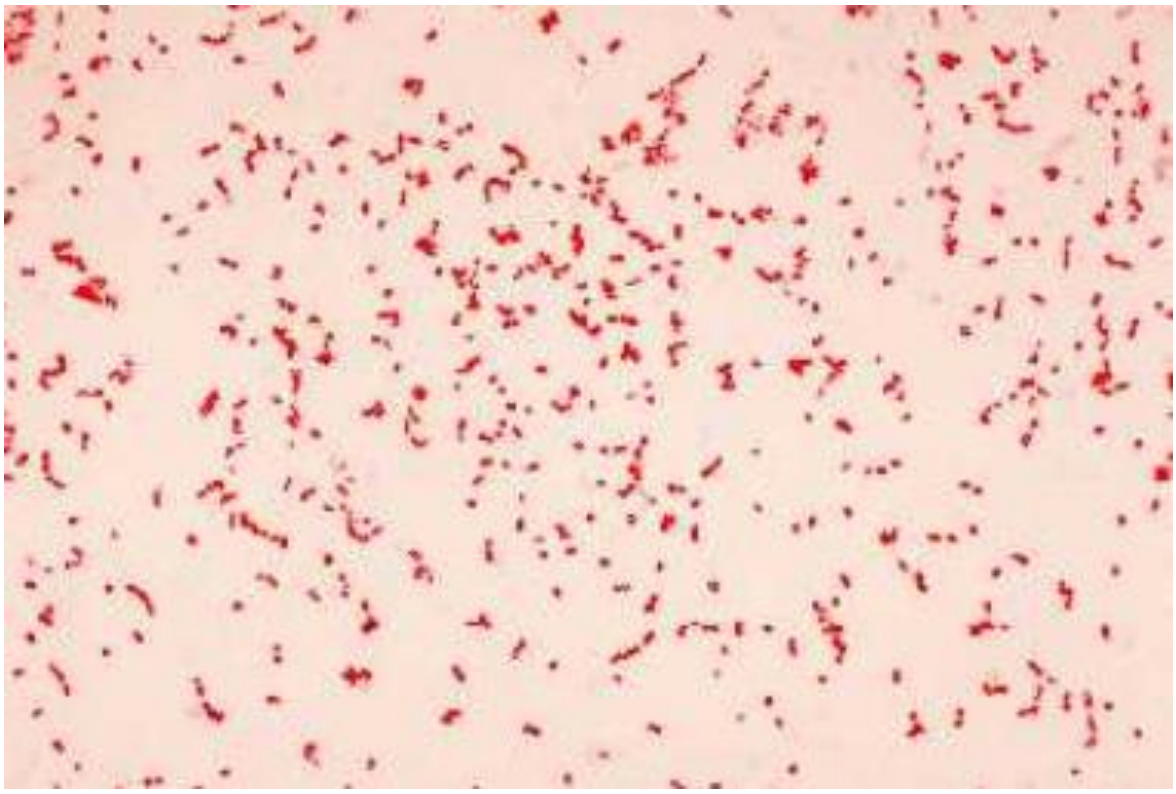


Figure 6: Gram stain appearance of Acinetobacter baumannii

Microbiology

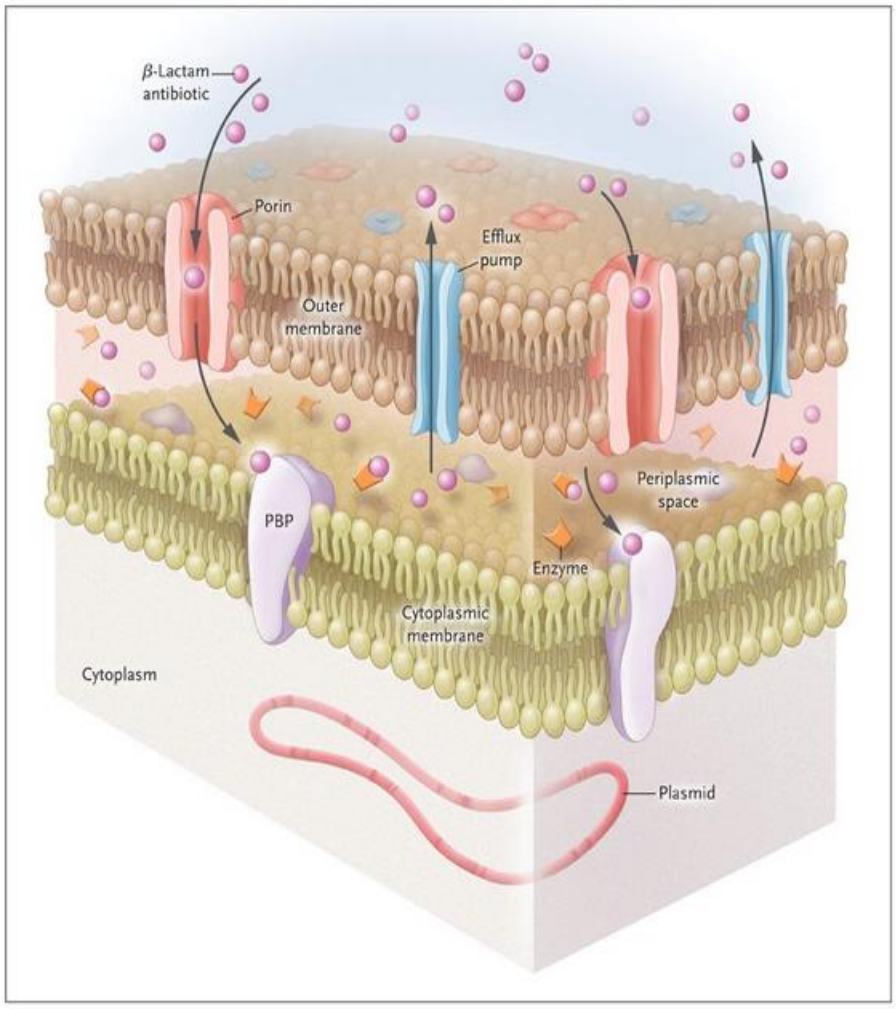
This organism was first isolated in 1911 by Dutch microbiologist Beijerinck using a medium enriched with calcium acetate. He initially described it as Micrococcus calco-

aceticus. The name '*Acinetobacter*' was officially accepted in 1971 by the subcommittee on the Taxonomy of Moraxella and Allied Bacteria.(40)

Currently, the genus *Acinetobacter* comprises 'Gram-negative, strictly aerobic, non-fermenting, non-fastidious, non-motile, catalase-positive, oxidase-negative bacteria with a DNA G+C content of 39% to 47%'. Of the 26 named species and nine genomic species in the genus, the medically significant ones have often been referred to as the A. calco-aceticus complex. This comprises of four phenotypically similar organisms (Ac calco-aceticus, A. baumannii, *Acinetobacter* genomic species 3 and *Acinetobacter* genomic species 13TU) which cannot be further differentiated from one another.(41) Of these, the most common and medically important pathogen is the *Acinetobacter* baumannii.

The natural habitat of members of the *Acinetobacter* genus is thought to be ubiquitous as it is found in most samples of soil and water. As a pathogen it usually targets mucous membranes, and its ability to form biofilms over invasive devices makes the chronically ill ICU patient an easy target. (41). In addition the ability of *Acinetobacter* to remain viable despite weeks of exposure to dry hostile environments without desiccation, makes it a dangerous organism once introduced into a setting with critically ill patients where spread through fomites can have disastrous consequences.(42)

Mechanisms of drug resistance



Antimicrobial Resistance in Acinetobacter.

Acinetobacter, like other gram-negative bacteria, has an outer membrane and a cytoplasmic membrane, between which (the periplasmic space) β-lactamases (carbapenemases, AmpC β-lactamases, and extended-spectrum β-lactamases) reside. Penicillin-binding proteins (PBPs), located at the level of the cytoplasmic membrane, constitute the final targets of β-lactam antibiotics. To bind to these targets, antibiotics must traverse the outer membrane through porin channels (outer-membrane proteins) into the periplasmic space. Once in the periplasmic space, β-lactam antibiotics bind to PBPs or are actively expelled from the bacterial structure through efflux pumps. Acinetobacter can harbor integrons and transposons, genetic elements on the bacterial chromosome or on plasmids, that can carry multiple cassettes with resistant genes (e.g., extended-spectrum β-lactamases and metallo-β-lactamases).

Acinetobacter develops resistance to antibiotics by multiple mechanisms. They are known to develop resistance to quinolones by mutations in the genes gyrA and parC and can also develop aminoglycoside resistance by the same genes.

AmpC b-lactamases are chromosomally encoded cephalosporinases seen in all members of the *Acinetobacter* genus. In normal circumstances, these enzymes have a low level of expression. But the insertion of a promoter sequence next to this gene causes overexpression thus leading to increased production of the cephalosporinase, leading to cephalosporin resistance.

Acinetobacter has also been known to acquire b-lactamases, including serine and metallo-b-lactamases, which leads to resistance to Carbapenems.

Bacterial efflux pumps cause decreased antibiotic concentration in the periplasmic space, thus decreasing the dose of available effective antibiotic. To cause a clinically significant effect, these efflux pumps usually work in concert with b lactamases or other enzymes that inactivate, or modify the antibiotic action. Efflux pumps have been implicated in resistance to quinolones, tetracycline's, chloramphenicol and tigecycline.(42)

Epidemiology and Clinical importance

As has been elucidated earlier, the organism *Acinetobacter* has been known for a long time, but the recent interest in it is due to the increasing incidence of hospital acquired infections, especially those with *Acinetobacter* infections. A 2008 report form the National Healthcare safety network estimated the frequency of gram negative bacteria associated health care associated infection. They found that *Acinetobacter* accounted for 8.4% of the Ventilator associated pneumonias and 2.2 % of all catheter related blood stream infections.(43)

There also appears to be an increasing incidence of multi drug resistance among the isolates of *Acinetobacter*. One study performed in Turkey between 2003-2007 found increase in incidence of Imipenem resistant isolates form 43.3% at the beginning of the study to 72.9% at the end of the study period.(44) Similar data was observed from an analysis of the Taiwanese nationwide surveillance database between 2003-2008 which found an increase in incidence of carbapenem resistant *Acinetobacter* baumannii from 4% to 62%(45).

The increase in incidence of drug resistant *Acinetobacter* is important because, the acquisition of drug resistant isolates have been linked to increased mortality and increased length of hospital stay. (46) These in turn have economic implications in the form of increased cost of hospital care, in addition to increased cost due to the higher level of antibiotics required for clearance of the infection. An estimate of the economic burden of *Acinetobacter* infection in the intensive care setting found that the mean increase in length of stay was 25.23±10.59 days with an estimated cost per bed per day of $4397.50 (range $1000-$8000) in the United States.

Hence there is an urgent need to combat this infectious agent with effective treatment and preventive strategies.

Current treatment options and future implications

In the case of antibiotic susceptible isolates of *Acinetobacter* baumannii, the treatment options are many and they include broad spectrum cephalosporins such as Ceftazidime. Beta lactamase inhibitor especially sulbactam has been shown to be highly effective against *Acinetobacter* and the combination of Ampicillin Sulbactam has been suggested to be at least as effective as Imipenem in susceptible isolates. (47)

Carbapenems are another effective class of drugs that have a good bactericidal effect against *Acinetobacter* baumannii although the recent emergence of carbapenemase producing organisms has limited their clinical utility.

Polymyxins, especially Colistin are being widely used as the agents of choice against *Acinetobacter* isolates that are resistant to the first line agents. Although there have been no randomised control trials to test the efficacy of this drug, a review of nine observational trials have estimated a cure rate of 66% with Colistin(48). But the dosing difficulties and associated renal toxicities have been major hindrances to their widespread use.

Tigecycline has also been tried as a therapeutic option in multidrug resistant and extensively drug resistant *Acinetobacter* isolates. In one retrospective study among patients with multidrug resistant *Acinetobacter* baumannii infections, Tigecycline was associated with a good outcome among 81% of the patients.(49). This drug rapidly enters the tissues after administration and thereby has very low serum concentrations. Hence it is not advised to use this drug for patient with *Acinetobacter* bacteraemia, as it can lead to inadequate drug levels and impaired clearance of the organism thus facilitating development of drug resistance.

Empirical antibiotic therapy is required in most clinical situations and the use of combination drugs for coverage of the broadest range of antibiotic susceptibility is a prudent option. Knowledge of the local antibiotic susceptibility profiles is essential for a rational choice of empirical therapy. For an area that is known to have multi drug resistant strains the use of combinations consisting of a Polymyxin or a Carbapenem would be a reasonable choice.

LACUNAE IN CURRENT KNOWLEDGE AND RATIONALE FOR THE STUDY

Although infection with *Acinetobacter* has been linked to increased mortality, the causal association has not been definitively proved. Since these infections commonly affect patients in a critical care setting, the pre-morbid state of the host, the multiple comorbid illnesses, prolonged exposure to antibiotics and invasive devices are all factors that need to be considered in the event of mortality. Hence the debate of whether the *Acinetobacter* is just a coloniser in an already critically ill host versus *Acinetobacter* being the final definitive agent that caused the mortality has not been completely resolved.

A systematic review of six matched case-control and cohort studies demonstrated a significant increase in mortality rate among those with *Acinetobacter* infection or colonisation, compared with others. (50) Another single center cohort study done by Robenshtok et al compared the mortality rates among 112 patients with *Acinetobacter* bacteraemia with 90 patients with Klebsiella bacteraemia. They found an increased mortality of 22.7% among the *Acinetobacter* group even after adjusting for possible confounders.(51) This study seems to demonstrate that *Acinetobacter* infections have a poor prognosis when compared to Klebsiella bacteraemia. However the possibility that they have not adjusted for a possible significant unknown confounder still remains.

The debate also extends to the question of whether the increased mortality observed among those with *Acinetobacter* infections can be attributed to the organism itself or the presence of drug resistance. Kwon and colleagues compared the mortality rates among patients with Imipenem resistant isolates of *Acinetobacter* with those who had Imipenem sensitive isolates of the same organism. They found an excess mortality of 25% among those with Imipenem resistant *Acinetobacter* bacteraemia.(52) On the other hand, a more recent study done in Thailand found no statistically significant difference in mortality rates between Imipenem resistant and Imipenem susceptible isolates on multivariate analysis after controlling for the confounding effects of severity of illness, inappropriate antibiotic therapy and primary source of bacteraemia. (53)

It is not known whether the contradictory results of the studies can be attributed to just methodological differences, or whether they are due to differences in the characteristics of the patient populations and the standards of care available to them.

There are no Indian studies which address the question of attributable mortality due to *Acinetobacter* infections.

There is also a lack of data regarding the antibiotic susceptibility profile of *Acinetobacter* baumannii from the institution where this study was carried out.

Hence this study was done to address the above inadequacies in knowledge.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study is a prospective cohort study among adult patients in Intensive Care Units (Medical ICU/ Medical HDU/Surgical ICU) who develop a hospital acquired infection (VAP or CR-BSI) as per the criteria defined below.

Describe the setting

Setting:

This study was conducted at a tertiary care teaching hospital in South India. Most of the patients who are admitted in the critical care wards (MICU, MHDU, and SICU) arrive through the Accident and Emergency department. The Surgical ICU (SICU) also has post-operative patients who are stabilised before shifting back to the wards. The population served by this hospital is very varied. There are a large number of patients who travel from all parts of India for medical care at this facility. In addition, this serves as a referral centre for many local hospitals as well. Hence the population of patients in this centre reflects a population distributed through the whole of India.

Participants

Adult patients admitted in the MICU, MHDU and SICU from January 1, 2013 to June 30, 2014

Inclusion criteria:

Above the age of 16 years

Exclusion Criteria:

Infections with Coagulase negative Staphylococci

Methodology:

Case Ascertainment:

Any patient who developed fever 48 hours after admission to the Intensive care unit was evaluated for VAP/BSI. Detailed physical examination was performed and appropriate blood investigations (total WBC count, differential WBC count, procalcitonin, arterial blood gas analysis), cultures (blood, urine, and endo-tracheal aspirate), Urine routine analysis and radiological investigations (chest X-Ray, ultrasound abdomen etc.) were undertaken to identify the source of the infection. The principal investigator also performed a clinical examination to determine any possible sources of infection. All the investigations were followed up carefully by the principal investigator to determine if the patient fulfilled the criteria for diagnosis of VAP or CRBSI.

If patient fulfilled the criteria of VAP or BSI, then they were classified as study participants. After obtaining informed consent from the family members, the clinical details of the patient were entered into the clinical research form.

The study participants whose clinical isolates grew *Acinetobacter* were classified as cases, while those whose clinical isolates grew other non-*Acinetobacter* organisms were classified as controls.

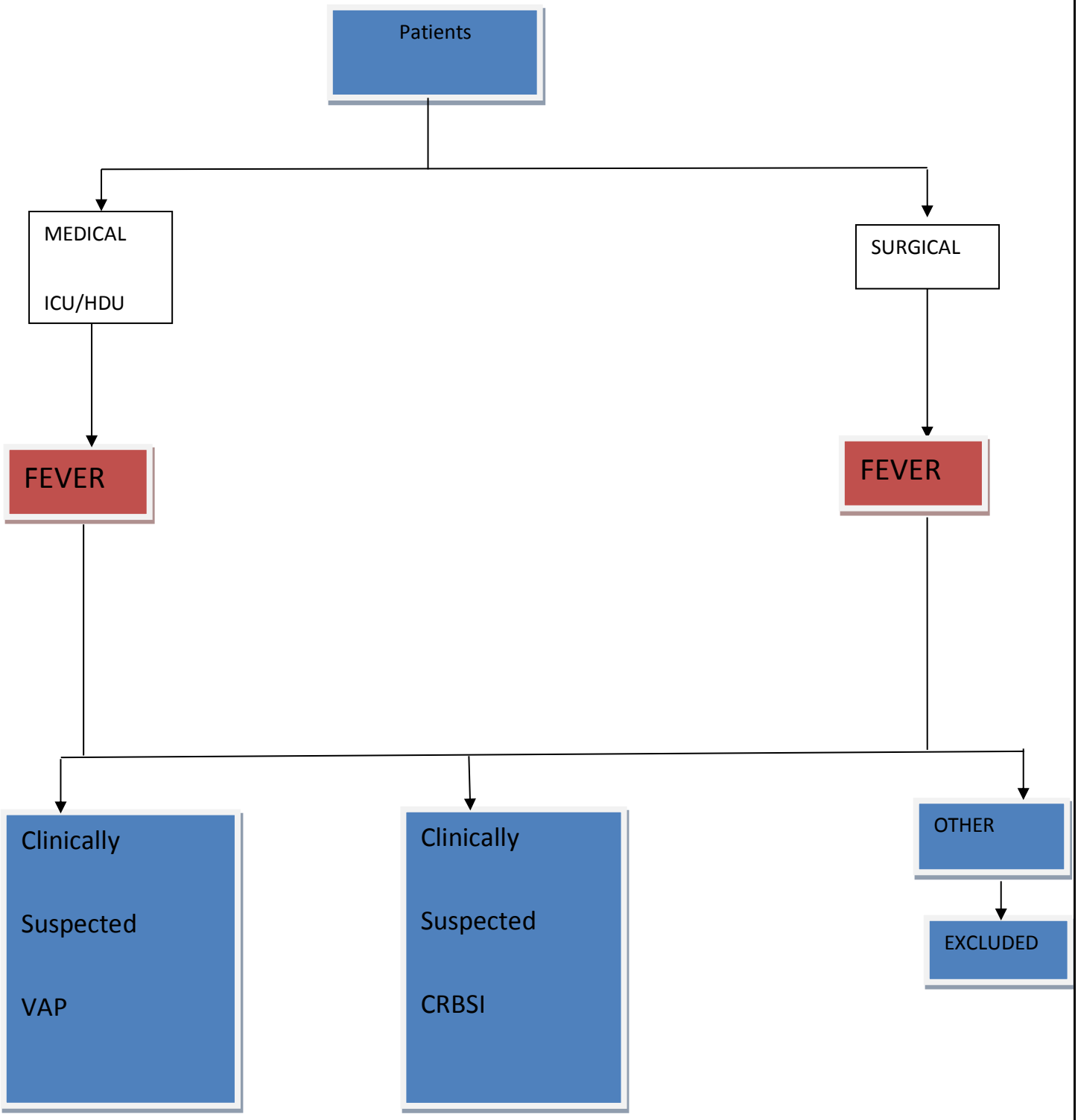
If the culture grew more than one organism of which one was *Acinetobacter*, the patient was still classified as belonging to the *Acinetobacter* group (case). Only those patients for whom none of the organisms on culture grew *Acinetobacter* species were classified into the Non-*Acinetobacter* group.

The patient was followed every day until the final outcomes of death or discharge were attained. During the period of follow up the antibiotics used, the duration of antibiotic use, and the microbiological data on the organism and their antibiotic susceptibility profile was noted.

If, during the course of hospital stay the patient developed another event of fever and fulfilled criteria for VAP or CRBSI, then the details were entered as a separate event, and followed up accordingly. Hence a single patient could have more than one HAI event during the course of a single hospital stay.

If, during the course of the evaluation, it is found that the initial fever was caused due to a focus other than the lung or the CVC, then the patient was excluded from the study.
The study methodology was evaluated and approved by the institutional review board (IRB min No: 8159 dated 9.9.2013).

The overall algorithm for the study methodology is depicted below:


Patients
MEDICAL
ICU/HDU
SURGICAL
FEVER
FEVER
Clinically
Suspected
VAP
Clinically
Suspected
CRBSI
OTHER
EXCLUDED

CRBSI Case definition:

A patient was suspected to have CRBSI based on the following criteria:

- Patient has indwelling vascular catheter

  AND

- Fever >100.4F OR hypothermia <97.7 F

  AND

- Culture from both venous blood and vascular catheter with same organism

  OR

- Culture from both venous blood and the catheter tip with the same organism

  AND

- No other source evident for the bacteraemia.

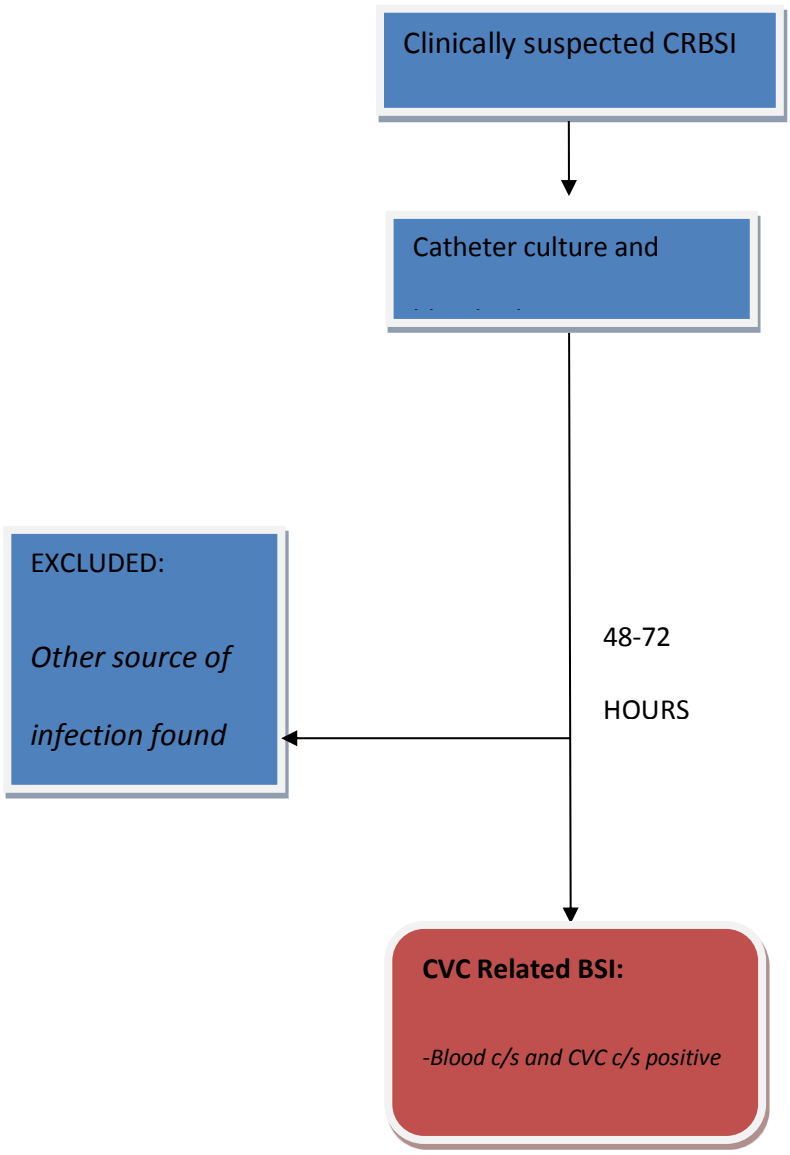
Other additional criteria for definition of CR-BSI:

If the blood culture had significant growth of organism, but the central line culture was not sent, or did not have any growth, but the clinical suspicion of CRBSI was high enough to warrant change of line site.

If the central line culture had significant growth of organism (>15cfu) but the venous blood culture was negative (no growth), but the clinical suspicion of CR-BSI was high enough to warrant change of line site.

The patients with BSI are further classified based on the blood and CVC cultures as *Acinetobacter* species infection or Non-*Acinetobacter* species infections.

The following flow chart is the algorithm for a suspected CRBSI.

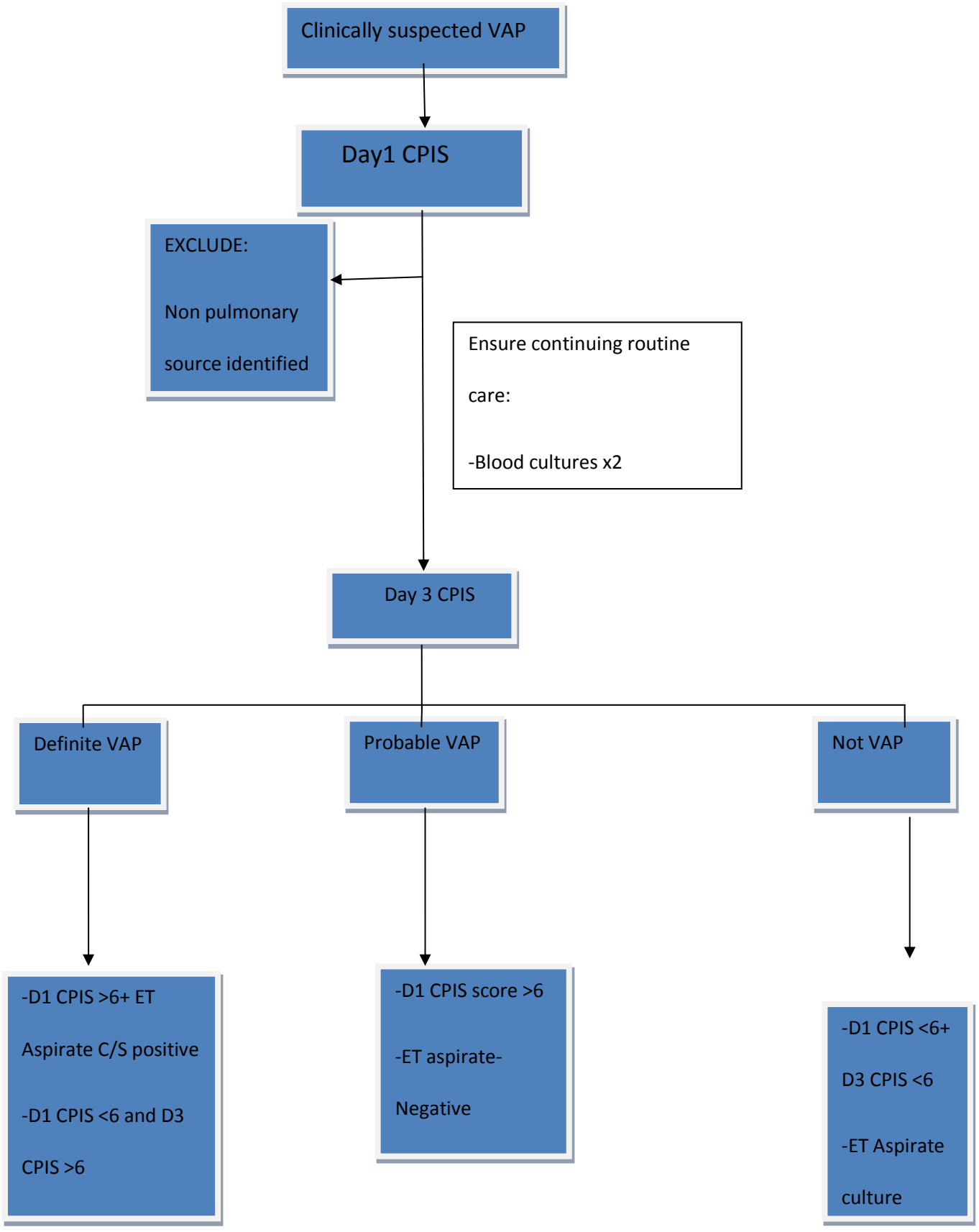


VAP Case definition:

If the patient was clinically suspected to have a VAP, then the Clinical Pulmonary Infection Score (CPIS) was calculated. A score more than 6 was highly suggestive of a VAP. Appropriate tracheal aspirate and blood cultures were taken as per the normal protocol in the ICU. The patient was reassessed again at 72 hours and a repeat CPIS score was calculated. The results of the ET aspirate were also followed up by this time. Based on the two CPIS scores and the ET aspirate, the patient was classified as having 'definite VAP', 'probable VAP' and 'no VAP' only those who fulfilled criteria for 'definite VAP' were included as cases in the study.

Based on the growth from the ET aspirate the patients were classified as *Acinetobacter* species and non *Acinetobacter* infections.

The following flowchart is an algorithm for a suspected VAP.



Outcome Assessment:

Primary Outcome:

The primary outcome was to compare the mortality rate between cases (*Acinetobacter* infection) and Control (Non-*Acinetobacter*) among VAP and CRBSI.

All patients enrolled in the study were followed up until the outcome of death or discharge was achieved.

For the purpose of this study, the patients who were discharged against medical advice were analysed with the outcome of 'death'.

Secondary Outcome

Microbiological outcomes:

Since this was the first study which looked at infections caused by the *Acinetobacter* species, baseline microbiological data such as the incidence of *Acinetobacter* associated

VAP and CR-BSI was collected. This data was used to estimate the proportion of VAP and CR-BSI caused by *Acinetobacter* species.

The antibiotic susceptibility profiles of the *Acinetobacter* isolates were also documented and analysed.

Clinical Outcomes:

- The Duration of ICU stay- measured in days from entry to ICU to either death or discharge to the wards and the duration of hospital stay- measured in days from entry to the hospital to death or discharge from the hospital was calculated and documented for both groups. This was later analysed to determine the duration of stay in each group.

- Duration of ventilation- measured as ventilator free days.

  Ventilator- free days (VFD) was defined as number of days between successful weaning from mechanical ventilation and day 28 after initiation of mechanical ventilation (VFD= 28- No of days on the ventilator). If the patient required mechanical ventilation beyond 28 days or if the patient died during the course of hospital stay the number of VFD was taken as 0.

  Successful weaning was defined as a continuous period of 48 hours or more off mechanical ventilation.

Sample Size Calculation:

As per a recent study (unpublished) done in our institution, among patients admitted in MICU/MHDU by another investigator, the rates of VAP was found to be ~ 10%. (15 cases out of 146 patients included over 6 months). Based on this data we expected about 75 patients with VAP over our proposed study period of 17 months.

Another study published from our ICU showed VAP to have a mortality rate of about 52.7%. Assuming a 20% difference in mortality between the two groups, the sample size was calculated as shown below:

Two Proportion - Hypothesis Testing - Large Proportion - Equal Allocation

Proportion in group I = .50

Proportion in group II = .30

Risk difference = 0.2

Power (%) = 80

Alpha Error (%) = 5

Side = 2

Required sample size for each arm = 93

Alpha Error (%)	Power (%)	Sample Size (n)
	70	73
5	80	93
	90	124

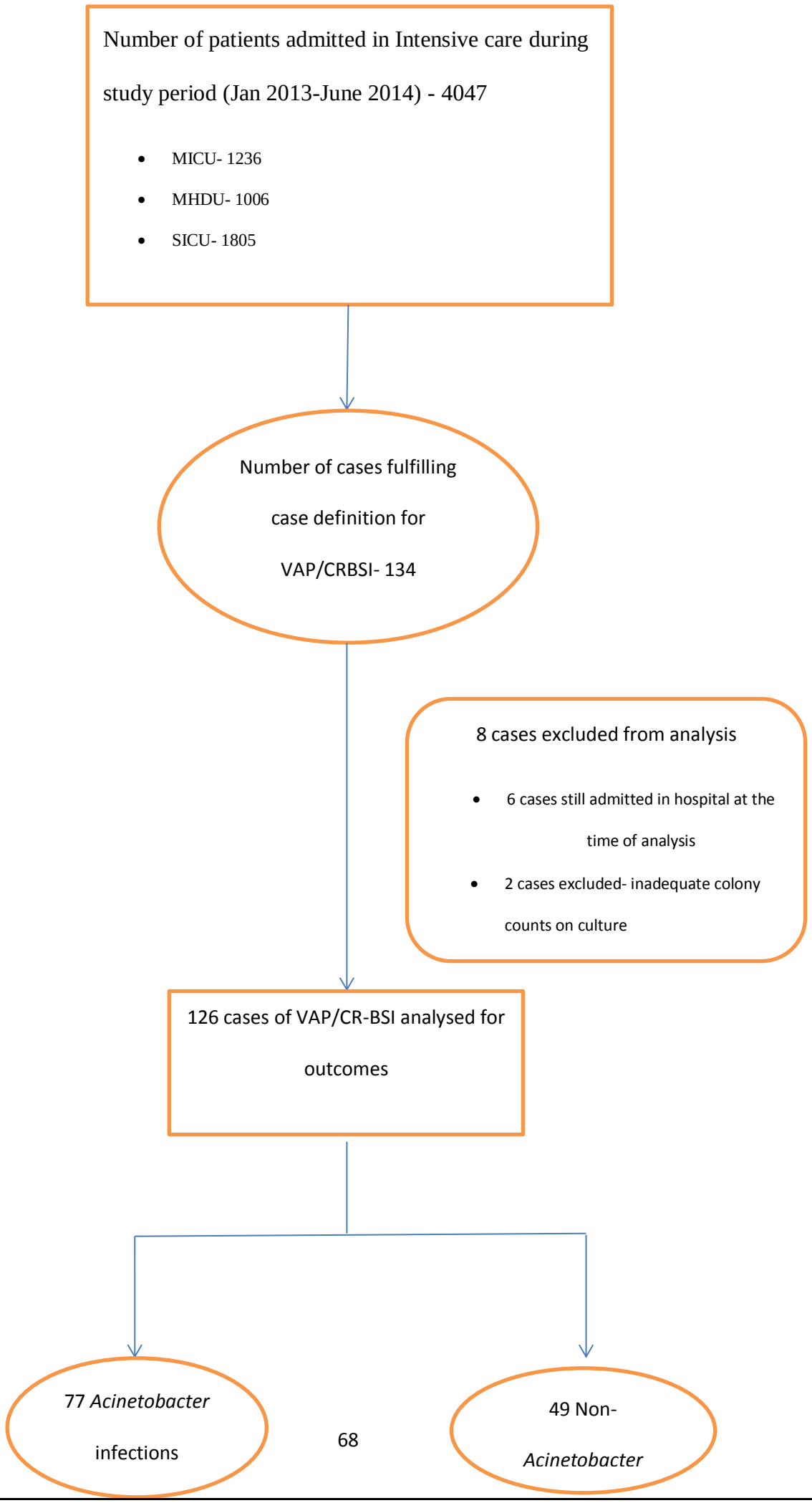
Therefore 93 patients in each arm would yield a power of 80% at an alpha error of 5% to detect a 20% difference in mortality between the two groups. We calculated t-test, Chi-square test and ANOVA as appropriate for all analysis. Odds Ratio (OR) and confidence intervals (CI) were calculated and a 'p' value <0.05 was considered significant. Data was entered using Epi Data version 3.1 and analysed using SPSS version 22.

RESULTS

RESULTS

Patient Characteristics:

From January 2013 to June 2014 a total of 4047 patients were admitted in the intensive care units (MICU/MHDU/SICU) out of which 134 patients fulfilled the case definitions for VAP or CRBSI as defined earlier. 2 patients were subsequently excluded from the study because although they fulfilled the criteria for a VAP, the colony counts of the sputum culture were low, and hence the microbiological diagnosis of VAP was questionable. 6 patients were excluded from the current analysis since they were still admitted in the hospital during the time of analysis and hence could not be included for the primary outcome measurement. Therefore a total of 126 patients were analysed as shown in the figure.


Number of patients admitted in Intensive care during study period (Jan 2013-June 2014) - 4047
MICU- 1236
MHDU- 1006
SICU- 1805
Number of cases fulfilling case definition for VAP/CRBSI- 134
8 cases excluded from analysis
6 cases still admitted in hospital at the time of analysis
2 cases excluded- inadequate colony counts on culture
126 cases of VAP/CR-BSI analysed for outcomes
77 Acinetobacter infections
49 Non-Acinetobacter

Comparison of baseline clinical characteristics:

A total of 126 patients developed the HAI's of interest during the study period, of which 77 patients developed *Acinetobacter* infections and the other 49 patients had Non- *Acinetobacter* infections.

The mean age of the patients in the *Acinetobacter* group was 46.5± 17.3 years while that of the Non-*Acinetobacter* group was 41.5± 17.4 years, with no statistically significant difference between the two groups. (p=0.11).

44 (56.4%) were male in the *Acinetobacter* group while 34(43.6%) were female in the Non-*Acinetobacter* group (p=1.9).

The median APACHE III scores at baseline between the *Acinetobacter* and Non-*Acinetobacter* groups of patients was 70 and 66 with inter quartile ranges of 47-96 and 39-83 respectively. Although there is no significant difference between the groups, it can be seen that the cohort of patients who eventually developed *Acinetobacter* related HAI during the course of their hospital stay had higher APACHE III scores indicating that they were more critically ill, at presentation, than the other group. (****mention statistics)

The median time to developing the HAI event was 7 days in both the groups, with no significant difference between them (p= 0.92). Similarly the median device day (the duration in days from insertion of the ET tube or vascular line to development of VAP or CRBSI

respectively), was also 7 days in both groups. This data suggests that the first week of hospital admission was the period of highest incidence of acquiring a HAI.

TABLE 2:

PATIENT CHARECTERISTICS AT BASELINE:

Characteristics	*Acinetobacter* group (N=77)	Non-*Acinetobacter* group (N=49)	95% CI	Significance P- value
Age (years)*	50, 29-62	41.46± 17.4	-1.1-11.4	0.11
Male (%)	44 (56.4)	34(43.6)		1.90
APACHEIII SCORE*	70,(47-96)	66, (39-83)	-2.2 – 19	0.12
Time to developing HAI (days)*	7, (5-9)	7, (4-13)		0.92
Device day at the time of HAI (days)*	7, (4-9)	7, 5-9		0.49

*Median, Inter Quartile Range.

Comparison of baseline comorbid conditions:

The comorbid illnesses of the patients in the two groups were compared and have been shown in table 3.

11 patients (14.3%) of those with *Acinetobacter* related HAI had an underlying lung disease (defined as the presence of underlying asthma, COPD, interstitial lung disease or other chronic lung disease) compared to 3 (6.1%) of those in the Non *Acinetobacter* group. This difference, however, was not found to be significant.

Among the patients with underlying heart disease (defined as the presence of Ischemic Heart disease, Rheumatic Heart disease or Chronic Heart failure) 10 patients (12.9%) belonged to the *Acinetobacter* group compared to 6 patients (12.2%) in the non *Acinetobacter* group, which was not significantly different.

22 (28.5%) and 10 (20.5 %) patients were diabetics in the *Acinetobacter* and Non *Acinetobacter* group, with no significant difference between them.

10 patients (12.9%) and 7 patients (14.3%) in the *Acinetobacter* and Non- *Acinetobacter* group were chronic alcohol consumers. 16 patients (20.7%) and 5 patients (10.2%) of the patients were Hypertensive among the *Acinetobacter* and Non- *Acinetobacter* groups respectively. None of these were found to be significantly different between the two groups.

TABLE 3: COMORBID ILLNESSES AT PRESENTATION (PRIOR TO DEVELOPING THE HAI):

Characteristics	*Acinetobacter* group (N-77)	Non-*Acinetobacter* group (N-49)	95% CI	Odds Ratio	Significance P- value
Diabetes	22 (28.5%)	10 (20.4%)	0.62-4	1.56	0.41
Hypertension	16 (20.7%)	5 (10.2%)	0.72-7.8	2.3	0.19
Underlying lung disease*	11 (14.3%)	3 (6.1%)	0.6-12.3	2.5	0.15
Underlying Heart disease**	10 (12.9%)	6 (12.2%)	0.3-3.6	1.07	0.88
Chronic alcohol use	10 (12.9%)	7 (14.3%)	0.29-2.86	0.953	0.9

*Asthma or COPD or ILD or other chronic lung disease

** Rheumatic Heart Disease or Ischemic heart disease or chronic heart failure

Comparison of baseline diagnosis:

A comparison was done between the two groups, of the most common syndromes and presumptive diagnoses at the time of admission (refer table 4).

33 patients (42.9%) and 8 patients (16.3%) in the *Acinetobacter* and Non-*Acinetobacter* groups respectively were admitted with infections (this included syndromic diagnosis such as sepsis or septic shock even if the source was not identified at the time of admission).

There was a significantly higher proportion of 'infection' related syndromes in the *Acinetobacter*-related HAI group. The most common infections in this patient cohort were found to be scrub typhus and pneumonias (which could be community acquired pneumonias, or infective exacerbations of COPD).

The other syndrome which was found to be significantly more common in the Non *Acinetobacter* group of patient was 'poisoning/overdose'. Only 13 patients (16.9%) of those in the *Acinetobacter* group had come due to a poisoning or drug overdose compared to 17 (34.7%) patients in the Non-*Acinetobacter* group. Most of the patients had presented with consumption of an Organophosphorous compound

The numbers of the patients with other diagnoses were not significantly different between the two groups.

TABLE 4: BASELINE DIAGNOSIS

Syndromes	*Acinetobacter* group (N-77)	Non-*Acinetobacter* group (N-49)	95% C I	Significance P- value
Infection	33 (42.9%)	8 (16.3%)	1.6-9.3	<0.001
poisoning/overdose	13 (16.9%)	17 (34.7%)	0.16-0.9	<0.05
surgical/trauma	12 (15.6%)	10 (20.4%)	0.28-1.8	0.48
Neoplastic	4 (5.2%)	4 (8.2%)	0.14-2.6	0.75
Others	15 (19.5%)	10 (20.4%)	0.38-2.30	0.95

Comparison of antibiotics given prior to developing HAI:

The antibiotics given prior to the onset of the HAI were compared between the two groups (Refer Table 5).

21 patients (27.2%) with *Acinetobacter* related HAIs received macrolides while only 4 patients (8.1%) with non- *Acinetobacter* related HAIs had received prior macrolides. Azithromycin was the most commonly used macrolide. The significant difference in usage of Azithromycin may be attributed to the previously noted difference in proportion of patients with infection related diseases admitted in the two groups.

Regarding the use of Carbapenems among the *Acinetobacter* group, 35 patients (45.4%) had received prior Carbapenems in the hospital compared to 14 patients (28.5%) of those in the Non-*Acinetobacter* group. This difference was found to have a trend towards significance.

There was no significant difference in the use of other classes of antibiotics between the two groups.

TABLE 5: COMPARISON OF ANTIBIOTICS GIVEN PRIOR TO HAI

Antibiotic groups	*Acinetobacter* group (N-77)	Non-*Acinetobacter* group (N-49)	95% confidence interval, Odds Ratio	Significance P- value
BL/BLI*	49 (63.6%)	26(53%)	0.33-5.52, 1.5	0.23
Carbapenem	35(45.4%)	14(28.5%)	0.91-4.82, 2.08	0.08
Macrolides	21(27.2%)	4(8.1%)	1.24-15.72, 4.2	<0.05
Aminoglycosides	8(10.3%)	7(14.28%)	0.21-2.3, 0.7	0.707
Tetracycline	5 (6.4%)	2 (4.08%)	0.26-12.73, 1.63	0.705
Fluoroquinolone	5 (6.4%)	6 (12.2%)	0.12-1.99, 0.5	0.336
BL**	5 (6.4%)	5 (10.2%)	0.14-2.61, 0.61	0.509
Teicoplanin	5 (6.4%)	4 (8.16%)	0.17-3.70, 0.78	0.735
Colistin	4 (5.19%)	6(12.24%)	0.09-1.69, 0.39	0.185

**Beta lactam with Beta lactamase inhibitor*

*** Beta lactam*

Comparison of baseline laboratory results at the time of enrolment:

The baseline Laboratory results at enrolment (at the time of acquiring the HAI) were compared between the two groups and are shown in Table 6.

The median total leukocyte count was 12050 and 13400 cells/cu.mm among the *Acinetobacter* and non-*Acinetobacter* group respectively. The median lactate in mmol/L was 1.7 and 1.3 among the two groups respectively. The median P/F ratios 241 and 234 mmHg respectively and the median Creatinine was 0.9mg/dl in both the groups.

None of the baseline laboratory values had any significant difference between the groups at the time of developing the Hospital Acquired infection.

TABLE 6:

Characteristics	*Acinetobacter* group (N-77)	Non- *Acinetobacter* group (N-49)	p- value
Total Leukocyte counts (cells/cu mm) Med, IQR	12050, (9700-18400)	13400, (9800-19500)	0.59
Lactates (mmol/L) Med, IQR	1.7, (1.2-2.5)	1.3, (1.1-2)	0.14
P/F ratio (mm Hg) Med, IQR	241, (169.5-340)	234, (148.7-338.2)	0.29
Creatinine (mg/dl)	0.9, (0.8-1.5)	0.9, (0.6-1.4)	0.21

Other additional descriptive characteristics:

Distribution of Non-Acinetobacter related Hospital Acquired Infections

Analysis of the clinical isolates of the 49 patients who had a non *Acinetobacter* related hospital acquired infection was done (refer Table 7)

The most common Non-*Acinetobacter* organism in the clinical isolates was Klebsiella and Pseudomonas both of which were cultures in 23 of the isolates, forming 46.9% of the total number. The next most common organism was E-coli which was cultures in 11 isolates constituting 22.4%.

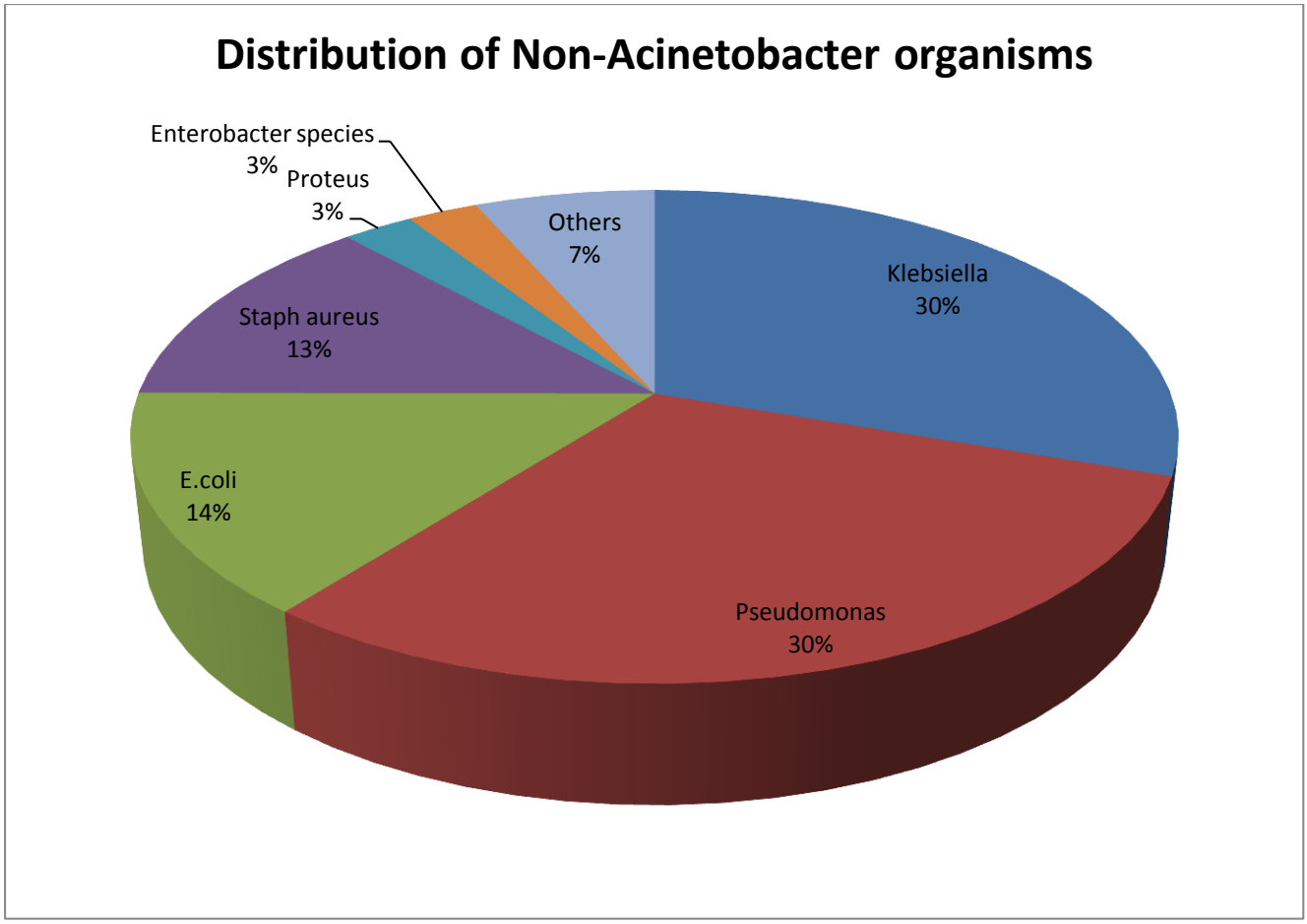
Staphylococcus aureus was cultured in 10 isolates constituting 20.4%. As will be demonstrated in the following tables, the majority of Staph aureus isolates were obtained from central line related infections.

Proteus and enterobacter species formed a minority.

The other organisms that grew on culture include sternotrophomonas and one isolate that grew Streptococcus pneumonia which was not community acquired.

TABLE 7: DISTRIBUTION OF NON-*ACINETOBACTER* ORGANISMS

ORGANISM	FREQUENCY (IN CULTURE)	PERCENTAGE
Klebsiella	23	46.90%
Pseudomonas	23	46.90%
E.coli	11	22.40%
Staph aureus	10	20.40%
Proteus	2	4.00%
Enterobacter species	2	4.00%
Others	5	10.20%


Distribution of Non-Acinetobacter organisms
Enterobacter species
3%
Proteus
3%
Others
7%
Klebsiella
30%
Staph aureus
13%
E.coli
14%
Pseudomonas
30%

Distribution of organism by the type of Hospital Acquired Infection:

Those patients who developed a CR-BSI, the commonest causative organism was Klebsiella which grew in 12 of the cultures constituting 24% of all the isolates with CR-BSI.

Acinetobacter baumannii was isolated in 10 cultures, amounting to 20% of all the isolates.

7 cultures (14%) grew E.coli while 5 cultures (10%) grew Pseudomonas and another 5 cultures grew Staphylococcus aureus.

TABLE 7:

CR-BSI CAUSATIVE ORGANISMS:

ORGANISM	FREQUENCY (IN CULTURE)	PERCENTAGE
Klebsiella *spp*.	12	24%
***Acinetobacter* baumannii**	10	20%
E.coli	7	14%
Pseudomonas aeruginosa	5	10%
Staph aureus	5	10%
Enterobacter *spp*.	3	6%
Proteus *spp*.	3	6%
Others	5	10%

TABLE 8:

VAP CAUSATIVE ORGANISMS:

ORGANISM	FREQUENCY (IN CULTURE)	PERCENTAGE
***Acinetobacter* baumannii**	67	45.8%
Pseudomonas aeruginosa	34	23.2%
Klebsiella *spp*	20	13.6%
Staph aureus	12	8.2%
E.coli	9	6.1%
Others	4	2.7%

Among the patients who developed a VAP, *Acinetobacter* baumannii grew on 77 endotracheal tube aspirates. This constituted 45.8% of all the VAP organisms.

Pseudomonas was the second most common organism isolated constituting 23.2% of all isolates.

Klebsiella was found in 20 isolates constituting 13.6% while Staphylococcus aureus was isolated in 12 cultures constituting 8.2% of all the ET aspirate cultures.

A comparison of the above two tables clearly shows the predilection that *Acinetobacter* species shows towards pulmonary infections. The distribution of organisms causing VAP is dominated by the *Acinetobacter* group which by itself constituted almost half of all the VAP's observed in this cohort. This is in contrast to CR-BSI, where the commonest causative agent (Klebsiella) only constituted 20% of the isolates. This observation just reinforces the already established microbiological fact that *Acinetobacter* favours respiratory epithelium both for colonisation and infection.

OUTCOMES:

Primary Outcome:

COMPARISON OF IN-HOSPITAL MORTALITY RATES

TABLE 9:

HAI group	Death	Discharge
Acinetobacter infection	44 (57.1%)	20 (40.8%)
Non *Acinetobacter* infection	33 (42.9%)	29 (59.2%)

Total- 126

Odds ratio for death from *Acinetobacter*- 1.933 (0.935-3.99, P-value- 0.074)

INTERPRETATION:

Although the mortality was approximately two-fold higher among patients with *Acinetobacter* HAI when compared to no-*Acinetobacter* HAI, this difference was not statistically significant.

Secondary Outcomes:

Microbiological outcomes:

PROPORTIONS OF BSI AND VAP DUE TO *ACINETOBACTER*

TABLE 10

	Acinetobacter	**Non *Acinetobacter***
CR-BSI	10 (30.3%)	23 (69.7%)
VAP	67 (72%)	26 (28%)

67 patients (72%) of VAP's in this cohort were caused by *Acinetobacter* baumannii infection. On the other hand 23 patients (69.7%) of Cr-BSI were caused by a Non-*Acinetobacter* organism.

This feature of the majority of VAP being caused by *Acinetobacter* can be attributed to the fact that these bacteria are known to thrive in moist environments such as the respiratory tract.

The difference in VAP and CR-BSI occurrence among the *Acinetobacter* and Non-*Acinetobacter* organisms was found to be statistically significant (P value<0.001).

This implies that if a patient in a critical care setting develops a VAP, then empiric therapy should be targeted towards *Acinetobacter* species, since these form almost 70% of all the VAP's in this cohort.

ANTIBIOTIC SUSCEPTIBILITY PROFILE OF *ACINETOBACTER* SPECIES:

TABLE 11

Antibiotic classes	Sensitive	Resistant	Total isolates tested
AMINOGLYCOSIDES	31(14%)	190 (85.9%)	221
BL/BLI*	5 (2.9%)	162 (97%)	167
BETA LACTAMS	3 (1.4%)	208 (98.5%)	211
CARBAPENEM	2 (1.3%)	143 (98.6%)	145
CO-TRIMOXAZOLE	7 (10.2%)	61 (92.4%)	68
AZITHROMYCIN	0	2 (100%)	2
TETRACYCLINES	18 (24.6%)	55 (75.3%)	73
LEVOFLOXACIN	3 (3.9%)	73 (96%)	76
COLISTIN	74 (98.6%)	1(1.3%)	75

*Beta lactams-Beta lactamase inhibitors

Of all the *Acinetobacter* baumannii isolates, 85.9% were found to be resistant to aminoglycosides, 97% were resistant to BL/BLI and 98.5% were resistant to beta lactams. All isolates (100%) were resistant to Azithromycin and 96% were resistant to Levofloxacin.

Antibiotic susceptibility testing to Carbapenems showed a 98.6% resistance rate to Carbapenems.

98.6% of all the isolates were sensitive to Colistin, with only 1 isolate (1.3%) showing Colistin resistance.

Based on the above data it can be concluded that in the event of a VAP in a critically ill patient in this institution, the causative organism is very likely to be *Acinetobacter*. The empiric antibiotic therapy should include Colistin, which can be downgraded based on the specific sensitivity profile of the patient's isolate.

Clinical Outcomes:

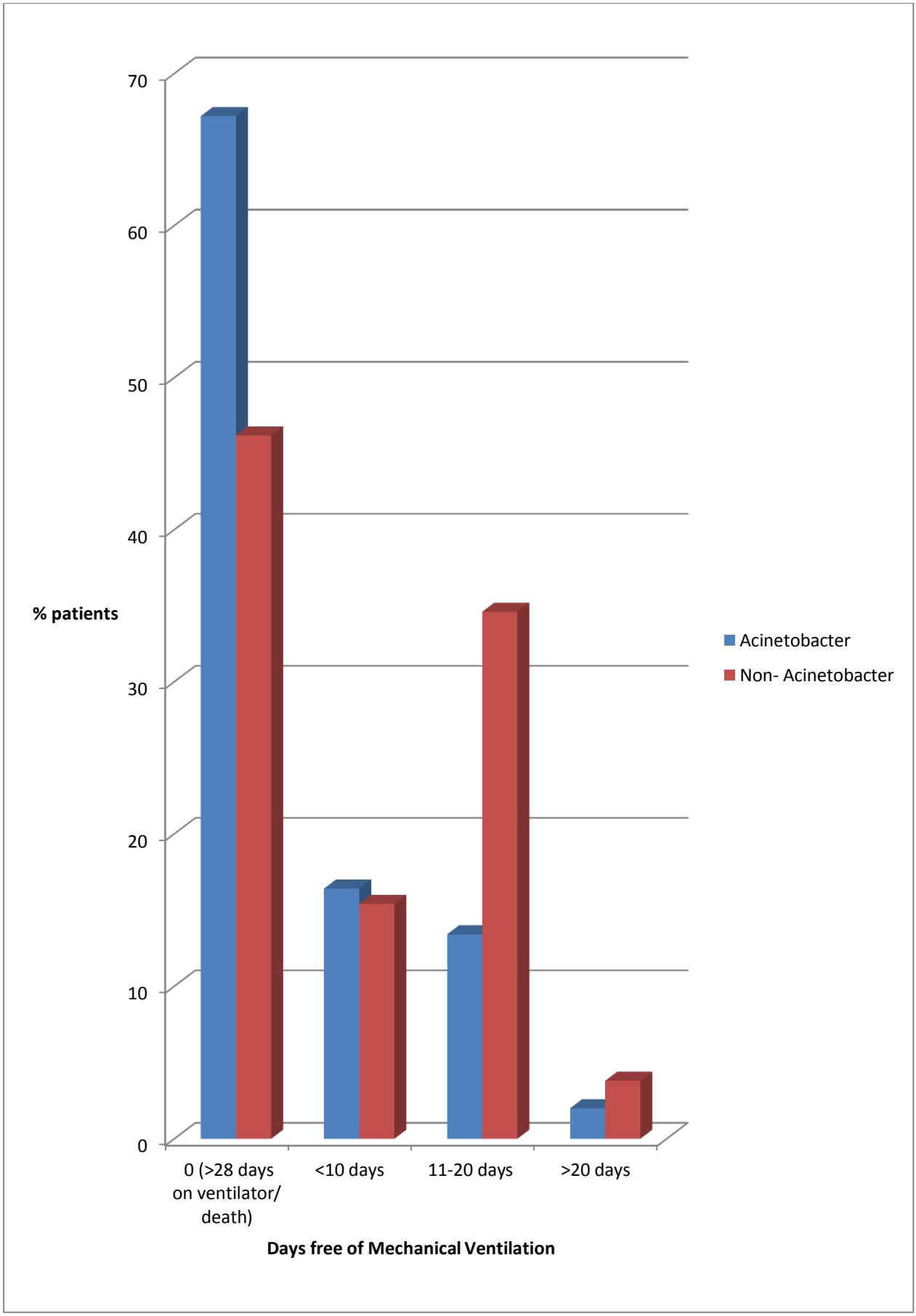
DURATION FREE OF MECHANICAL VENTILATION:

TABLE 12

days free from mechanical ventilation	*Acinetobacter* N (%)	Non- *Acinetobacter* N (%)
0 (>28 days on ventilator/ death)	45 (67.2%)	12 (46.2%)
<10 days	11 (16.4%)	4 (15.4%)
11-20 days	9 (13.4%)	9 (34.6%)
>20 days	2 (3%)	1 (3.8%)

Test of Significance:

Analysis of Variance between groups (p-value) = 0.035


70
60
50
40
30
20
10
0
% patients
Acinetobacter
Non- Acinetobacter
0 (>28 days on ventilator/ death)
<10 days
11-20 days
>20 days
Days free of Mechanical Ventilation

For those patients who developed a VAP, the duration of ventilator free days was calculated as per the protocol detailed earlier.

The proportion of patients with ventilator free days of 0 was higher in the *Acinetobacter* group as compared to the other group. This indicates a larger proportion of poor ventilator outcomes (in the form of prolonged mechanical ventilation >28 days or death during course of treatment in hospital) among those with *Acinetobacter* related VAP.

The group of patient with <10 days free of the ventilator in a month were also found to have a slightly higher proportion of *Acinetobacter* related HAI. Beyond 10 ventilator free days, this ratio was reversed.

The differences in ventilator free days was found to be statistically significant (p-value <0.05). Therefore it can be concluded that *Acinetobacter* HAI causes a significant increase in the duration of mechanical ventilation and poorer ventilator outcomes (prolonged ventilation >28 days or death).

DURATION OF ICU STAY AND DURATION OF HOSPITAL STAY:

TABLE 13

	Acinetobacter	Non-*Acinetobacter*	p-value
Duration of ICU stay	18, 13-28*	17,10-25	0.208
Duration of Hospital stay (days)	26, 16.2-46.5*	26, 15.5-37	0.76

* Median, Inter-Quartile range

The duration of ICU stay and Hospital stay was found to have no significant difference between the groups.

The median duration of ICU stay among the two groups was 18 days and 17 days for the *Acinetobacter* and Non-*Acinetobacter* groups respectively with no significant difference in the duration of ICU stay between the two groups.

Similarly the median duration of hospital stay in both the groups was 26 days and with no statistically significant difference between the two groups.

The lack of a significant difference in the duration of hospital stay and ICU stay has to be understood in the light of the previous finding of poorer ventilator outcomes. The results show that *Acinetobacter* associated VAP are associated with poorer ventilator outcomes (prolonged ventilation or death) with no significant increase in duration of ICU stay.

DISCUSSION

DISCUSSION

There is a global phenomenon of increasing rates of *Acinetobacter* species related hospital acquired infections. This is a ubiquitous organism with well-developed adaptive mechanisms to survive in a variety of environmental conditions. In the hospital environment *Acinetobacter* has been isolated from healthcare equipment, humidifiers, keyboards etc. and spread from person to person by hands of healthcare personnel. Their innate adaptability has led them to gain resistance to a wide variety of antimicrobial classes in a relatively short period of time. This has led to global alarm regarding the possible emergence of a pan resistant *Acinetobacter* 'super-bug'.

However, *Acinetobacter* species itself has none of the inherent virulence factors seen in a 'professional pathogen' such as Staphylococcus aureus. In addition, the usual hosts for an *Acinetobacter* infection are critically ill patients whose immune systems are probably already underperforming due to their underlying illness. So the important question that needs to be addressed is "what is the true mortality attributable to *Acinetobacter* after considering all the host factors and underlying disease factors in a critically ill patient?" This study was performed in an attempt to answer this question.

The cohort of patients included in this study consisted of critically ill adult admitted in the medical and Surgical ICU who developed a VAP or CR-BSI. The comparison of the baseline characteristics showed that the patients who eventually developed an *Acinetobacter* associated Hospital Acquired infection had a higher median APACHE III score at the time of admission. Although this difference was not statistically significant it is to be noted that this

organism tends to favour those who are more critically ill. This observation has been noted in other studies with *Acinetobacter* species.

The centre at which this study was conducted in Southern India is an area which is endemic for Scrub typhus and has a large proportion of patients presenting with severe scrub typhus related ARDS and other major organ involvement (hepatitis, acute kidney injury, myocarditis etc.) especially during the rainy season. These patients often require prolonged intensive care with mechanical ventilator support until they recover organ functions, but overall have a good prognosis and chance for a full recovery. Pneumonias constituted the other major infection in the *Acinetobacter* cohort. The common factor in both these diseases is the presence of lung injury. In both Scrub typhus and severe pneumonia there is a degree of lung damage that occurs. In addition, there is a severe systemic inflammation with ongoing immune system activation. In this setting, it can be hypothesised that the underlying lung damage and the ongoing inflammatory response could make these critically ill patients more vulnerable for an *Acinetobacter* VAP. The current study was not powered to answer this question, but it needs to be addressed in future studies on *Acinetobacter* associated VAP's.

This centre in Tamil Nadu is surrounded by areas of agricultural land. Organophosphates are pesticides which are freely available and hence commonly used as agents for deliberate self-harm. This is reflected in the large proportion of these patients in this study cohort. The patients with organophosphate poisoning commonly develop intermediate syndrome and require prolonged mechanical ventilation thus putting them at higher risk for the development of VAP. The significantly larger proportion of patients with poisoning/overdose in the Non-*Acinetobacter* arm could also partially explain the lower median age group in that arm since these patients are usually younger individuals.

The difference observed among the groups was the significantly smaller proportion of patients with 'poisoning' in the *Acinetobacter* group when compared to the Non-*Acinetobacter* group. Most of those who presented with poisoning had consumed an organophosphorous compound and required prolonged intubation and mechanical ventilation following the development of an intermediate syndrome. It has been hypothesised that Organophosphate compounds alter the cell mediated immunity such that there is a susceptibility to certain infections, especially Pseudomonas. In agreement with this observation, in our cohort of patients, those with organophosphorous poisoning predominantly developed infections with Pseudomonas and hence there was a significantly larger proportion of 'Non-*Acinetobacter* infections' seen.

Comparison of antibiotics given prior to the onset of HAI showed that those patients who eventually developed an *Acinetobacter* related HAI had received Macrolides more commonly than those who did not. We think this is probably secondary to the predominance of scrub typhus and pneumonias in the *Acinetobacter* arm, rather than any effect of the antibiotic itself. A study done in Thailand compared Azithromycin with Doxycycline in severe scrub typhus. The study showed greater efficacy of Azithromycin than doxycycline in the treatment of severe scrub typhus.(54) Based on this evidence the institution where this study was conducted has been implementing a protocol of combination therapy with Azithromycin and Doxycycline in severe scrub typhus. For severe pneumonias, the IDSA/ATS guidelines recommends empiric therapy with Azithromycin and a beta lactam or beta lactam combination with beta lactamase inhibitor.(55). This is the treatment guideline that is

implemented at this institution. This can explain predominance of Azithromycin use in the *Acinetobacter* group.

It is also important to note at this time the difference in Carbapenem use among the two groups. The *Acinetobacter* group had 35 patients (45%) who had already received Carbapenems prior to developing the HAI, as compared to 14 patients (28%) among those with Non-*Acinetobacter* related HAI. As per the Surviving Sepsis guidelines, in the event of severe sepsis of whatever cause, the empirical therapy of choice should include a carbapenem if a gram negative organism is suspected. The increased use of Carbapenems may once again reflect the severe of underlying illness among those who developed an *Acinetobacter* related HAI.

Therefore at baseline itself the patients who developed *Acinetobacter* related HAI's were more critically ill, with higher APACHE III scores at baseline, and were admitted more commonly with infectious diseases.

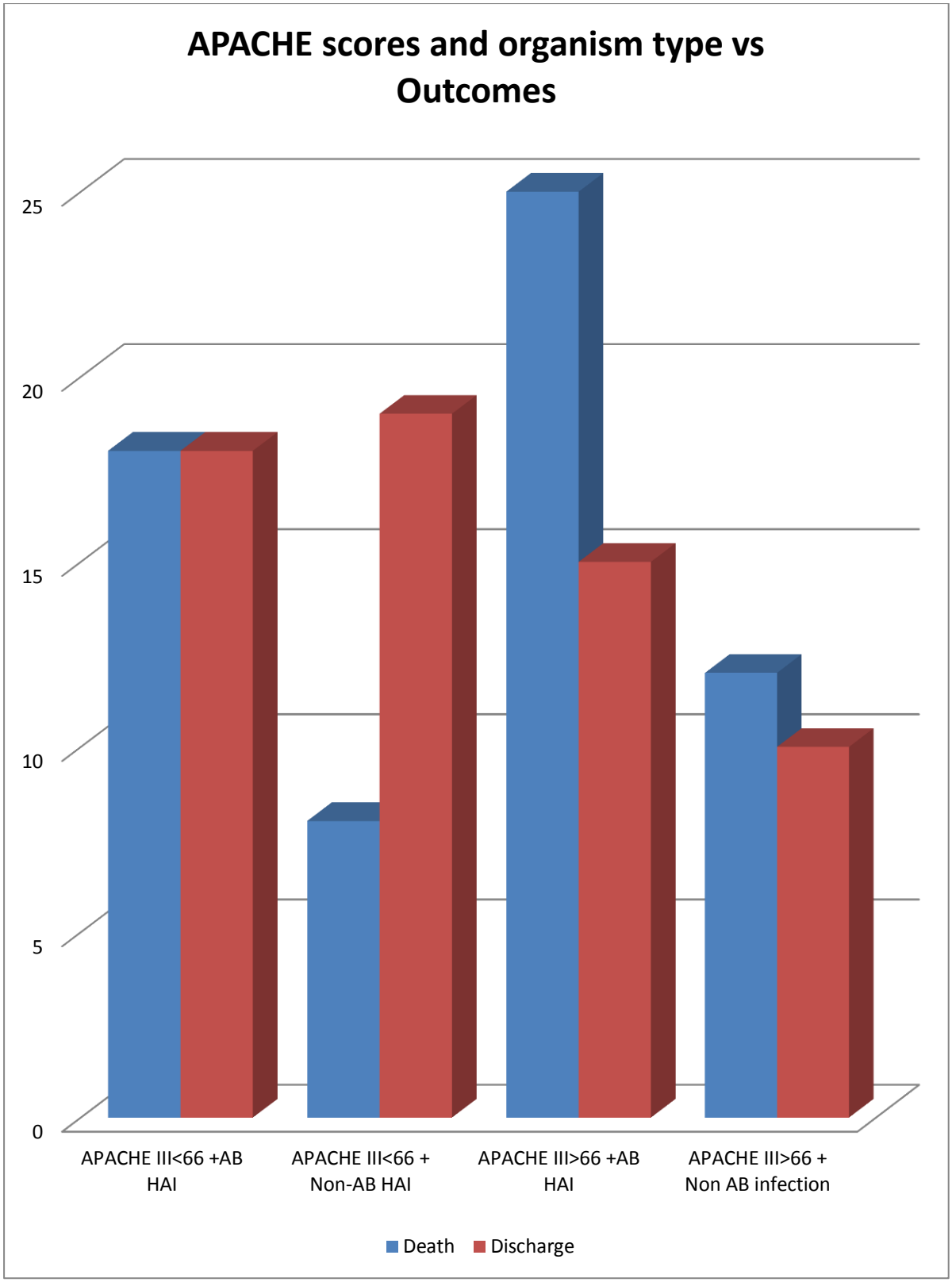
Primary outcome assessment showed that our cohort of patients with *Acinetobacter* related HAI did not have a significant difference in mortality when compared to those with a Non-*Acinetobacter* related HAI. Although the odds ratio of death was 1.9, the 95% CI was very wide and included the null value of 1. This suggests a trend towards higher mortality among HAI caused by *Acinetobacter spp*. A larger study is needed to confirm this finding.

Our hypothesis at the start of this study was that, since *Acinetobacter* is inherently a non-pathogenic organism, any mortality seen in these patients may be a factor of the critically ill state of the patients and not due to the infection.

In order to explore the possibility of underlying disease severity and host factors being a determinant of poor outcome among the HAI patients, we conducted univariate analysis of increasing APACHE III scores with mortality risk and compared them between *Acinetobacter* and Non-*Acinetobacter* species.

This additional analysis is presented below.

	Death	Discharge
APACHE III<66 +AB HAI*	18	18
APACHE III<66 + Non-AB HAI**	8	19
APACHE III>66 +AB HAI*	25	15
APACHE III>66 + Non AB HAI*	12	10


APACHE scores and organism type vs Outcomes
25
20
15
10
5
0
APACHE III<66 +AB HAI
APACHE III<66 + Non-AB HAI
APACHE III>66 +AB HAI
APACHE III>66 + Non AB infection
Death
Discharge

The comparison of baseline characteristics also did not show any statistically significant difference between the patients in the two groups.

This suggests that *Acinetobacter* was not the causative agent for the outcome, but the outcome was most probably determined by other host factors. Hence the conclusion can be made the determinant for outcome of death or discharge among the two groups is probably independent of the organism causing the HAI. The acquisition of *Acinetobacter* does not increase the mortality risk. The *Acinetobacter* could just be an agent causing infection in an already critically ill host, and is not the determinant of mortality.

This finding is in agreement with other studies (39,53) which have found that the comparative mortality of *Acinetobacter* related HAI is not significantly different from that caused by other organisms.

Jamulitrat et al conducted their study in Thailand and found that the mortality rate due to *Acinetobacter* bacteraemia was not significantly different from the mortality rate caused by infection with other organisms.(53)

However the results of our study results differ from that found by some other investigators (46,56). In the study done by Garcia et al, the mortality among *Acinetobacter* related HAI's was found to be significantly higher even after matching with APACHE III scores. (56).

One possible reason for this observed difference is the difference in patient characteristics. The studies that have found increase in mortality caused by *Acinetobacter* infections have been predominantly from developed countries (Spain, United States of America, Israel etc.) where the patient profile is different from that seen at our centre. Infections and poisonings/

drug overdose formed the majority of the admission diagnosis in our cohort. This is likely to be very different from the other studies.

Our study showed a significant increase in duration of mechanical ventilation but no increase in the duration of ICU and hospital stay.

The antibiotic susceptibility profiles of the *Acinetobacter* isolates in our cohort showed significant proportion of resistance to Carbapenems with susceptibility to Colistin. This is the first study in this institution to look at the antibiotic susceptibility of these isolates and hence provides good baseline data for future comparative studies.

The presence of such a high proportion of Carbapenem resistance is a matter of concern, especially since the only drug that seems to be sensitive is Colistin.

Even among Colistin isolates there was 1 patient who developed a Colistin resistant *Acinetobacter* infection. Further follow up studies will be required to evaluate the significance of this finding.

LIMITATIONS

LIMITATIONS

The calculated sample size was 93 in each arm, amounting to a total of 186 patients. Only 127 patients have been analysed for the purpose of dissertation at this time. Hence conclusions that have been made based on this data have to be taken with the consideration that this study is underpowered at this time.

A re-analysis done after achieving the required sample size may provide greater insight as to the true effect of *Acinetobacter* upon mortality.

This cohort included patients from both Medical as well as Surgical ICU. The APACHE III scores for all the patients were calculated based on their parameters at the time of admission to the hospital (prior to the onset of the HAI). Although this appropriately reflected the disease severity in the medical cohort of patients, it underestimated the disease severity in the surgical patients, especially those who were taken up for elective procedures and developed complications requiring prolonged ICU stay.

CONCLUSIONS AND RECOMMENDATIONS

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1. The proportion of HAI (VAP and CR-BSI) caused by *Acinetobacter spp*. In this cohort was 61%
2. *Acinetobacter* was the most common cause of VAP
3. Prior receipt of Carbapenems was associated with *Acinetobacter* infections
4. APACHE III scores were higher in patients who developed HAI due to *Acinetobacter spp*.
5. Patients with 'infectious syndromes' were more likely develop *Acinetobacter* HAI when compared to other syndromes needing admission to ICU
6. Almost all (98.6%) of the isolates of *Acinetobacter* were carbapenem resistant
7. Colistin resistance among *Acinetobacter* is rare
8. Mortality was two-fold higher among *Acinetobacter* HAI, though this difference did not achieve statistical significance
9. Patients with *Acinetobacter* HAI had poorer ventilator outcomes

In our cohort study of critically ill medical and surgical patients with VAP or CR-BSI, we found no significant increase in mortality rates among those with *Acinetobacter* related HAI's compared to those with Non-*Acinetobacter* related HAI. However we found that the patients with *Acinetobacter* related HAI's had significantly poorer ventilator outcomes (death or >28 days on Ventilator) but no significant increase in ICU or Hospital stay compared to those with Non-*Acinetobacter* related HAI. We also found that in our centre a large proportion of VAP were associated with *Acinetobacter*, and most of them were resistant to Carbapenems but susceptible to Colistin.

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ANNEXURES

Information Sheet

This sheet is for your information regarding a research project that is being conducted in the ICU.

During the period of stay of a patient within a hospital, it is possible to get new infections from the surroundings, nearby patients, or any equipment or devices that are used for the treatment of the patient. These infections are called Hospital acquired infections. Such infections can be harmful to that patient and can even be life threatening. Very little is known about these infections. This research study is being done in order to get a better understanding of Hospital Acquired infections especially in terms of what medicines (antibiotics) can be used, as well as the overall outcome of patients who get these infections.

One bacteria called Acinetobacter, has recently become a major cause for Hospital Acquired Infections. This study will be comparing the patients who have Hospital Acquired infections with Acinetobacter with those who have Hospital Acquired Infections due to other bacteria.

For this study we will be carefully noting down the details of the patient such as the duration of fever, the results of tests (like total counts, Creatinine, Procalcitonin etc) sent from the ICU as well as images (like Chest X ray). We will also be noting down details about previous illnesses that the patient had (such as Diabetes, Hypertension) which the patient had before being admitted in the ICU. We will also be noting down the causative organism for the Hospital Acquired Infection (Acinetobacter, E. Coli etc) and all the antibiotics being given to the patient as well as the duration of antibiotic use. We will be following up these details until the end of the patient's stay in the hospital.

All the information that we collect from the patients will be kept strictly confidential, and no personal details about the patient will be revealed to any third party. Only the persons involved in the analysis of the data from the study will have access to the medical and laboratory records of the patient

As explained above, this study only involves observation and recording of test results and medications given to the patient. No procedure will be done upon the patient apart from the routine care being provided to them from the ICU. There will be no risk of injury or harm to the patient due to their participation in this study.

There will be no financial compensation for the patient or his/her family as well as no additional costs (other than the costs of routine ICU care) to the patient or family due to their participation in this study.

The participation of the patient in this study is purely voluntary and he/she is free to withdraw from the study at any time. Refusal to participate in this study will not result in any change in treatment given to the patient, any penalty, or any loss of benefits to which the patient is otherwise entitled

For further questions kindly contact Dr Ajoy Oommen John , Department of Medicine CMC Vellore, Ph no: 7639195315.

Consent form

Study Title: comparison of clinical outcomes of Hospital acquired infection (Ventilator Associated Pneumonia and Catheter related blood stream infections) among Acinetobacter spp with other bacterial pathogens among critically ill patients at a tertiary care centre in South India

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

Clinical Research Form

Name: **Age:** **Sex: Male / Female**

Address:

Contact number:

PRIMARY ADMISSION / RE-ADMISSION

Date of hospital admission:

Date of ICU admission: **Discharge date:**

Diagnosis at admission:

Day of ICU admission at the time of recruitment:

APACHE-III Score at the time of recruitment:

Risk factors/Co-morbidities: (Circle features present at admission)

Asthma	COPD	Other chronic lung disease
Diabetes	Ischemic heart disease	Chronic heart failure
Rheumatic heart disease	Chronic renal failure	Chronic liver disease
Hypothyroidism on treatment	Hyperthyroidism	Anaemia
Autonomic dysfunction	HIV infection	Phaeochromocytoma

Illicit drug use	Anti-cholinergic drug use	Alcohol
Others (list)		

ANTIBIOTICS RECEIVED PRIOR TO RECRUITMENT: 1. 2. 3. 4. 5.

Date of first fever: CVC Day:___ ET Tube Day:_____

Infection type: **BSI/ VAP**

Date								
Total WBC count								
Differential count								
Procalcitonin								
Blood lactate								
Urine routine analysis								
Creatinine								
eGFR								

Chest Xray			

CULTURES	1	2	3	4

BLOOD				
CATHETER				
ET ASPIRATE				
OTHERS				
ANTIBIOTICS AFTER HAI: 1 . 2. 3. 4. 5.				

Outcome: **Death/Discharge**

Duration of Ventilator free days :

Duration of ICU stay:

Duration of hospital stay:

CPIS SCORE FOR VAP:

Variable	Point
Temperature • 36.5 to 38.4 • 38.5 to 38.9 • ≥39.0 and ≤36.0	 0 1 2
Total WBC • 4,000 to 11,000 • <4,000 or >11,000 • <4,000 or >11,000 plus band forms ≥500	 0 1 2
Oxygenation • >240 or ARDS • ≤240 and no ARDS	 0 2
Tracheal secretions • None or scanty • Abundant • Abundant and purulent	 0 1 2
Chest x-ray • No infiltrate • Diffuse or patchy infiltrate • Localized infiltrate	 0 1 2
Tracheal aspirate culture • Pathogenic bacteria cultured in rare or light quantity or no growth • Pathogenic bacteria cultured in moderate or heavy quantity • Same pathogenic bacteria seen on Gram stain	 0 1 2

CRITERIA FOR BSI:

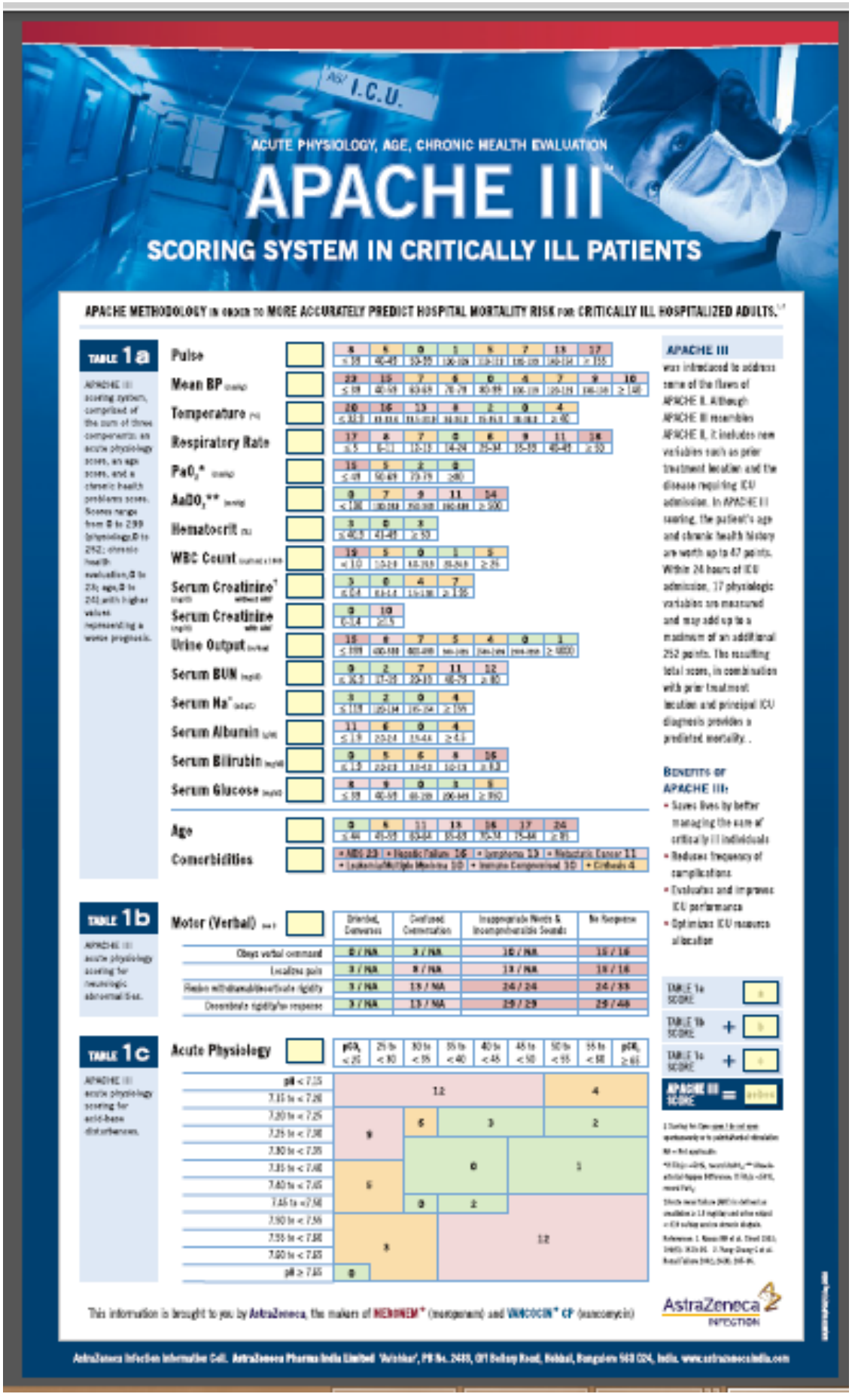
1) Patient has indwelling vascular catheter

AND

2) Fever (100.4F) OR hypothermia ,97.7C
3) Culture from both venous blood and vascular catheter with same organism OR
4) Culture from both venous blood and the catheter tip with the same organism

AND

No other source evident


ACUTE PHYSIOLOGY, AGE, CHRONIC HEALTH EVALUATION
APACHE III
SCORING SYSTEM IN CRITICALLY ILL PATIENTS
APACHE METHODOLOGY IN ORDER TO MORE ACCURATELY PREDICT HOSPITAL MORTALITY RISK FOR CRITICALLY ILL HOSPITALIZED ADULTS.
TABLE 1a
Pulse
Mean BP
Temperature
Respiratory Rate
PaO2*
AaDO2**
Hematocrit
WBC Count
Serum Creatinine*
Serum Creatinine
Urine Output
Serum BUN
Serum Na+
Serum Albumin
Serum Bilirubin
Serum Glucose
Age
Comorbidities
• AIDS 23 • Hepatic Failure 16 • Lymphoma 13 • Metastatic Cancer 11
• Leukemia/Multiple Myeloma 10 • Immune Compromised 10 • Cirrhosis 4
TABLE 1b
Motor (Verbal)
Obeys verbal command
Localizes pain
Flexion withdrawal/abnormal flexion rigidity
Decerebrate rigidity/no response
TABLE 1c
Acute Physiology
pH < 7.15
7.15 to < 7.20
7.20 to < 7.25
7.25 to < 7.30
7.30 to < 7.35
7.35 to < 7.40
7.40 to < 7.45
7.45 to =7.50
7.50 to < 7.55
7.55 to < 7.60
7.60 to < 7.65
pH ≥ 7.65
APACHE III
was introduced to address some of the flaws of APACHE II. Although APACHE III resembles APACHE II, it includes new variables such as prior treatment location and the disease requiring ICU admission. In APACHE III scoring, the patient's age and chronic health history are worth up to 47 points. Within 24 hours of ICU admission, 17 physiologic variables are measured and may add up to a maximum of an additional 252 points. The resulting total score, in combination with prior treatment location and principal ICU diagnosis provides a predicted mortality. .
BENEFITS OF APACHE III:
• Saves lives by better managing the care of critically ill individuals
• Reduces frequency of complications
• Evaluates and improves ICU performance
• Optimizes ICU resource allocation
TABLE 1a SCORE
TABLE 1b SCORE
TABLE 1c SCORE
APACHE III SCORE
This information is brought to you by AstraZeneca, the makers of MERONEM® (meropenem) and VANCOCIN® CP (vancomycin)
AstraZeneca
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